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08:37:38

1 RENO, NEVADA, WEDNESDAY, JANUARY 15, 2020, 8:34 A.M.

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08:34:12 3
08:34:12 4 THE COURT: Good morning. Please be seated.
08:34:14 5 Counsel, are you ready to resume?

08:34:18 6 MR. REIG-PLESSIS: Yes, Your Honor. Good
08:34:18 7 morning.

08:34:22 8 Good morning, Dr. Sheinberg.

08:34:24 9 THE WITNESS: Good morning.

08:34:30 10 REIG-PLESSIS: Mr. Gross, could we pull up
08:34:34 11 DDX 1.15.

12 JONATHAN I. SHEINBERG, M.D.,
13 recalled as a witness on behalf of the Defendant,
14 Previously sworn, testified further as follows:

08:34:21 14 DIRECT EXAMINATION RESUMED

08:34:21 15 BY MR. REIG-PLESSIS:

08:34:37 16 Q Dr. Sheinberg, on the screen right now is DDX 1.15, which
08:34:41 17 is a question and answer from the deposition of Amarin's
08:34:45 18 regulatory expert, Dr. Peck, in which Dr. Peck was asked, "And
08:34:49 19 is the indicated use of Vascepa limited to chronic use," to
08:34:54 20 which Dr. Peck replied, "No, I don't think so."

08:34:57 21 Dr. Sheinberg, were you in the courtroom when
08:35:02 22 Mr. Klein showed this testimony from Dr. Peck during opening
08:35:06 23 statements?

08:35:06 24 A Yes, I was.

08:35:07 25 Q And were you in the courtroom when Mr. Klein showed this

08:35:10 1 testimony to Dr. Budoff during cross-examination yesterday?

08:35:13 2 A Yes, sir, I was.

08:35:14 3 Q And did you hear Dr. Budoff disagree with Dr. Peck's
08:35:18 4 testimony that's on DDX 1.15?

08:35:20 5 A Yes, I did.

08:35:21 6 Q Do you agree with Dr. Budoff or Dr. Peck on this point?

08:35:26 7 A I agree with Dr. Peck.

08:35:28 8 As my testimony yesterday will indicate, this
08:35:33 9 medication does not need to be used in a chronic fashion. It
08:35:37 10 does have short-term efficacy and usage.

08:35:42 11 In fact, some of the data that's already been
08:35:44 12 discussed supports that. If we can refer to the MARINE trial,
08:35:49 13 there was -- if we all can think back and remember, and I
08:35:52 14 believe we can probably put up some of the demonstratives.

08:35:56 15 But in the MARINE trial, which was, according to
08:35:59 16 Dr. Budoff, designed to eliminate those individuals who would
08:36:02 17 have a short-term, reversible cause of hypertriglyceridemia
08:36:07 18 with the four to six-week washout phase, and then a two to
08:36:11 19 three-week triglyceride stabilization phase, we even, within
08:36:15 20 that trial, if you look at the placebo arm in individuals who
08:36:20 21 did not receive medication, there was still a 21 percent group
08:36:24 22 within that placebo arm who were able to reach triglycerides
08:36:27 23 below 500 simply with diet and exercise alone.

08:36:31 24 So my testimony yesterday and today supports the
08:36:34 25 fact that this can be a medication that is used not in the

chronic setting. In other words, we can use it in short, intermittent dosing.

MR. REIG-PLESSIS: I just want to break down what you said.

Mr. Gross, could you pull up DX 1701, page 42, please, and if we could go to the second to last paragraph above the footnote starting with the objective of the MARINE study.

BY MR. REIG-PLESSIS:

Q And, Dr. Sheinberg, do you recognize this as the public FDA medical review that we discussed yesterday?

A Yes, I do.

Q Dr. Sheinberg -- and actually --

MS. KEANE: Objection, Your Honor. My understanding is that this discussion of the specifics of the MARINE study is outside the scope of Dr. Sheinberg's --

THE COURT: I'm sorry, I'm not able to hear you.

MS. KEANE: Yes, Your Honor.

This discussion is outside the scope of Dr. Sheinberg's expert report.

MR. REIG-PLESSIS: Your Honor, I disagree.

Dr. Sheinberg discussed the design of the MARINE study, including the four to six diet and exercise washout period in paragraph 91 of his report.

He also cited both the FDA medical review of

08:37:48 1 this document and the MARINE clinical study report throughout
08:37:51 2 his rebuttal expert report, and, obviously, the design of this
08:37:55 3 study as well as this document was extensively testified to by
08:38:00 4 Dr. Budoff to whom Dr. Sheinberg is testifying in rebuttal.

08:38:04 5 MS. KEANE: Your Honor, I don't disagree that he
08:38:09 6 cited the medical review, but he did not discuss the specifics
08:38:15 7 with respect to the design of the MARINE study and how that
08:38:18 8 affected the ultimate results. That's not within the scope of
08:38:22 9 this report.

08:38:23 10 THE COURT: Mr. Reig?

08:38:23 11 MR. REIG-PLESSIS: I would just say again,
08:38:25 12 paragraph 91 of Dr. Sheinberg's report specifically -- is
08:38:30 13 actually devoted entirely to the fact that there was a four to
08:38:33 14 six-week diet and lifestyle stabilization period before the
08:38:37 15 beginning of the 12-week period. That's in his report.

08:38:39 16 And then paragraph 125 actually discusses and
08:38:42 17 addresses in fact the very point that Dr. Peck testified to,
08:38:47 18 that that could be one possible consistent reading of the
08:38:51 19 phrase before initiating icosapent ethyl on the labeling.

08:38:55 20 THE COURT: I would like to see the report and
08:38:57 21 the reference paragraph.

08:39:06 22 MR. REIG-PLESSIS: Permission to approach?

08:39:08 23 THE COURT: Yes. Am I looking at paragraph 91
08:39:16 24 and 125?

08:39:17 25 MR. REIG-PLESSIS: Yes, Your Honor.

08:40:20 1 THE COURT: (Court reviews document.)

08:40:32 2 MS. KEANE: And, Your Honor, I'll note as you're
08:40:34 3 reviewing the report, there's no discussion of this 21 percent
08:40:38 4 number that Dr. Sheinberg is purporting to testify to.

08:40:45 5 THE COURT: Well, the report, beginning at
08:40:48 6 paragraph 89, Dr. Sheinberg discussed the clinical data and
08:40:56 7 the MARINE trial, so he does reference the details of the
08:41:01 8 trial.

08:41:04 9 And then paragraph 125, he rebuts Dr. Budoff's
08:41:13 10 opinion about the 12-week period from the time that Vascepa is
08:41:18 11 prescribed to the follow-up visit.

08:41:20 12 So at least reading the paragraphs I've just
08:41:23 13 read, it appears to me that Dr. Sheinberg did reference the
08:41:26 14 MARINE study, the details of the study, as well as what
08:41:29 15 supports his opinion in disagreeing with Dr. Budoff.

08:41:33 16 So, is the objection still that the testimony
08:41:35 17 exceeds the scope of his expert report?

08:41:38 18 MS. KEANE: Yes, Your Honor. I believe it does.
08:41:41 19 In particular, the passage that Mr. Reig is showing to
08:41:45 20 Dr. Sheinberg is not cited in any of the sections that counsel
08:41:48 21 has cited in particular in paragraph 125.

08:41:53 22 I don't disagree that he included some
08:41:56 23 information about the design of the study, but no where did he
08:41:59 24 get into a discussion of the passage or the 21 percent -- the
08:42:04 25 21 percent number with respect to the placebo arm.

08:42:07 1 THE COURT: And I'm going to overrule the
08:42:09 2 objection. You can cross-examine him on that issue.

08:42:13 3 MS. KEANE: Okay. Thank you, Your Honor.

08:42:14 4 MR. REIG-PLESSIS: Thank you, Your Honor.

08:42:16 5 And, Mr. Gross, if we could just highlight the
08:42:19 6 sentence starting with "after a four- to six-week diet."

08:42:19 7 BY MR. REIG-PLESSIS:

08:42:25 8 Q Dr. Sheinberg, how do patients become eligible for
08:42:29 9 inclusion in the 12-week MARINE study?

08:42:32 10 A They were placed on a four- to six-week diet and
08:42:34 11 lifestyle stabilization phase and then a two-week -- what was
08:42:38 12 called the triglyceride qualifying period at which time all
08:42:42 13 patients who were ineligible for the study were weeded out
08:42:42 14 allowing the remaining patients to continue into the study.

08:42:47 15 And it was the thought by Dr. Budoff that this
08:42:52 16 period here, which would be from six to nine weeks prior to
08:42:56 17 the initiation the actual random -- the actual randomization
08:43:01 18 and utilization of medication was enough to remove the
08:43:05 19 individuals who had transient or short-term
08:43:10 20 hypertriglyceridemia.

08:43:11 21 Q Now, were the patients who qualified for the MARINE study
08:43:14 22 after this four to six weeks of diet and exercise within the
08:43:18 23 scope of the MARINE indication for Vascepa?

08:43:20 24 A Yes.

08:43:21 25 MR. REIG-PLESSUS: So, Mr. Gross, staying on

08:43:23 1 DX 1701, can we pull up page 51, please, and zoom in on figure
08:43:33 2 8 but include the first paragraph below the figure, please.

08:43:33 3 BY MR. REIG-PLESSIS:

08:43:39 4 Q And, Dr. Sheinberg, did all of the patients who qualified
08:43:41 5 for MARINE after four to six weeks of diet and exercise have
08:43:45 6 chronic genetic forms of severe hypertriglyceridemia that
08:43:48 7 require indefinite drug treatment?

08:43:51 8 A So I want to make sure I understand your question. So it
08:43:55 9 depends on who answers that question. I can answer it this
08:43:58 10 way.

08:43:58 11 According to Dr. Budoff, this -- the people who
08:44:03 12 qualified for the study would have been in that -- in that
08:44:07 13 group.

08:44:07 14 But my interpretation by looking at this is that is
08:44:09 15 not the case. There are people who were able to be enrolled
08:44:12 16 in the study who completed that wash-in period of diet and
08:44:17 17 stabilization and triglyceride stabilization who were
08:44:20 18 randomized to a placebo arm, in other words, they received no
08:44:24 19 medication, and in that placebo arm, 21 percent of those
08:44:28 20 individuals were able to get their triglycerides below
08:44:32 21 500 milligrams per deciliter by continuing to follow the
08:44:34 22 lifestyle modification plan that was set out in the initial
08:44:39 23 evaluation.

08:44:40 24 Q So were there patients in MARINE who had reversible,
08:44:43 25 short-term forms of severe hypertriglyceridemia?

08:44:46 1 A Absolutely, it's shown right there in the placebo arm.

08:44:49 2 Q And could those patients have benefitted from a short
08:44:53 3 course of Vascepa before diet and exercise took effect to
08:44:55 4 reduce their triglycerides below 500?

08:44:55 5 A Absolutely. And that's the major point that I mentioned
08:45:01 6 yesterday in which -- you know, in the trial here, which is a
08:45:05 7 big departure from what we do in the clinical setting.

08:45:10 8 In the clinical setting, if we see an individual
08:45:13 9 who's at risk for pancreatitis, which I think both sides have
08:45:16 10 agreed is a painful and life-threatening problem, we have
08:45:21 11 obligations as physicians to do everything we possibly can to
08:45:26 12 reverse that problem absolutely as quickly as we possibly can.

08:45:29 13 So we can wait -- in this case, this data is
08:45:35 14 generated at somewhere between 4 and 21 weeks, and this --
08:45:41 15 these individuals were able to get their triglycerides with
08:45:43 16 diet and exercise.

08:45:45 17 But if I have someone, you know, who has the risk
08:45:48 18 for pancreatitis, there's no way that I would want to wait 4
08:45:53 19 to 21 weeks to get that person down when we know that absolute
08:45:59 20 treatment with this medication, Vascepa, I see maximal
08:46:03 21 reduction of triglycerides within four weeks.

08:46:06 22 So if I have someone who is being treated to prevent
08:46:10 23 this life-threatening and incredibly painful process, and I do
08:46:15 24 a very conservative course, and I don't treat them, and that
08:46:20 25 person ends up getting pancreatitis, I have to answer to the

08:46:23 1 patient, the patient's family, I have to answer to my peers,
08:46:27 2 potentially the liability component of that, it's bad
08:46:31 3 medicine.

08:46:31 4 I would treat this person aggressively with as much
08:46:36 5 medication as I could possibly use up-front to reduce that
08:46:39 6 risk, and then, as shown here, it's very reasonable to stop
08:46:43 7 that medication after a short-term.

08:46:46 8 MR. REIG-PLESSIS: So, Mr. Gross, could we pull
08:46:47 9 up DX 2256 and go to page 2. Thank you, 2248 DX, and go to
08:47:32 10 the second page and zoom in on the dosage and administration
08:47:39 11 section, section 2, and could we highlight the second bullet,
08:47:49 12 please.

08:47:49 13 BY MR. REIG-PLESSIS:

08:47:58 14 Q And, Dr. Sheinberg, do you recognize this as the dosage
08:48:01 15 and administration section of the Vascepa label that we
08:48:04 16 discussed yesterday?

08:48:05 17 A Yes, I do.

08:48:06 18 Q Now, based on the MARINE data we just reviewed, if a
08:48:10 19 patient engages in appropriate nutritional intake and physical
08:48:14 20 activity before receiving icosapent ethyl for four to six
08:48:18 21 weeks, will that necessarily resolve any reversible causes of
08:48:22 22 severe hypertriglyceridemia?

08:48:25 23 A So I -- again, I want to make sure I answer your question
08:48:28 24 appropriately.

08:48:29 25 If patients engage in appropriate nutritional intake

08:48:33 1 and physical activity before receiving Vascepa, should -- can
08:48:36 2 you repeat the question, please?

08:48:38 3 Q Sure. Sorry, I think I misstated it.

08:48:39 4 If a patient engages in appropriate nutritional
08:48:43 5 intake and physical activity for four to six weeks, will that
08:48:47 6 necessarily resolve any reversible causes of severe
08:48:51 7 hypertriglyceridemia?

08:48:52 8 A Not necessarily. Sometimes it takes longer than that.

08:48:56 9 We saw that if the patients in -- as we saw here in
08:48:57 10 the MARINE trial, there were certain patients who, despite an
08:49:05 11 initial four- to six-week period, were still not able to get
08:49:07 12 their triglycerides lower than 500. It took them longer,
08:49:11 13 which was demonstrated throughout the duration of the study,
08:49:15 14 for them to get their triglycerides below 500.

08:49:18 15 Q And if a patient engages in appropriate nutritional
08:49:21 16 intake and physical activity for four to six weeks and still
08:49:25 17 has triglyceride above 500, does that necessarily mean that
08:49:28 18 that patient has a chronic, long-term cause of severe
08:49:32 19 hypertriglyceridemia?

08:49:33 20 A It does not.

08:49:34 21 MR. REIG-PLESSIS: So, Mr. Gross, can we go back
08:49:36 22 to DDX 4.43 which is where we left off yesterday.

08:49:36 23 BY MR. REIG-PLESSIS:

08:49:52 24 Q And, Dr. Sheinberg, beyond the 12 weeks limitations that
08:49:58 25 we discussed this morning and extensively yesterday, did you

1 also analyze another set of limitations in the asserted
2 claims?

3 A Yes, I did. The second limitation was a limitation
4 regarding specific lipid effects, in particular, a specific
5 percentage reduction in triglycerides, a neutral effect on LDL
6 cholesterol, and a reduction of apolipoprotein B.

7 Q So turning to DDX 4.44, what are the patent claims that
8 apply to your opinions on the lipid effect limitations?

9 A In regards to the minimum reduction in triglycerides, I
10 analyzed '715, patent claim 14, '560, patent claims 4 and 17,
11 '728, patent claims 1 and 16, '715, patent claim 14 --

12 I'm sorry. The next page -- the next section,
13 rather, I'm sorry, as I'm reading down with no increase in LDL
14 cholesterol, and that is the '728, claims 1 and 16, '715,
15 patent claims 14, '677, patent claims 1 and eight, '652,
16 patent claim 1, '560, patent claims 4 and 17.

17 In regards to the reduction in apolipoprotein B, the
18 three claims listed are '715, patent claim 14, '677, patent
19 claim 8, and '929, patent claim 5.

20 Q And just so the record is clear, what are the asserted
21 claims in which there is a minimum reduction in triglycerides
22 that's required?

23 A For example, at least ten percent, 20 percent, or a
24 statistically significant triglyceride reduction.

25 Q And what asserted claims does that apply to?

08:51:47 1 A '715, patent claim 14, and '560, patent claims 4 and 17.

08:51:55 2 Q So turning now to DDX 4.45, there's snapshot on the
08:52:01 3 screen of DX 2256, page 1. What are you showing on this
08:52:04 4 slide?

08:52:04 5 A This is the indications and usage section from the
08:52:07 6 defendants' package insert.

08:52:09 7 The highlighted area, which we've actually seen this
08:52:12 8 before, this shows that icosapent ethyl is indicated as an
08:52:16 9 adjunct to diet to reduce triglyceride levels in adult
08:52:19 10 patients with severe hypertriglyceridemia.

08:52:24 11 Q And does the indications and usage section encourage,
08:52:28 12 recommend, or promote administering defendants' products to
08:52:31 13 achieve the claimed lipid effects?

08:52:33 14 A It does not. It remains silent. It does not give any
08:52:36 15 direction towards a minimum percent triglyceride reduction.
08:52:40 16 It makes no mention of an avoidance in the increase of LDL
08:52:43 17 cholesterol, and it makes no mention of a reduction in
08:52:46 18 apolipoprotein B.

08:52:47 19 Q Now, are you aware of other drugs that are indicated to
08:52:51 20 control LDL-C and apo B levels?

08:52:54 21 A Yes, sir, absolutely.

08:52:56 22 Q So turning to DDX 4.46, there is a snapshot on the screen
08:53:01 23 of DX 1986, page 1. Could you identify this document.

08:53:05 24 A Yes, this is the package insert for Lipitor which is
08:53:10 25 atorvastatin. It's an oral cholesterol medicine that's been

08:53:15 1 around for quite some. It's known as a HMG-CoA reductase
08:53:20 2 inhibitor otherwise -- sorry.

08:53:20 3 THE COURT: And would you also make sure -- I
08:53:22 4 know you're sitting pretty close, but I want to make sure we
08:53:26 5 all can hear you as well.

08:53:28 6 THE WITNESS: Yes, ma'am.

08:53:29 7 So this is -- I'll start this slide again.

08:53:31 8 This is a label or package insert for Lipitor
08:53:35 9 which is the branded name of atorvastatin. Atorvastatin is
08:53:41 10 best known as a statin or an HMG-CoA reductase medication
08:53:47 11 which is designed specifically to reduce -- if you go to the
08:53:52 12 bottom bullet, it's designed and indicated to reduce total
08:53:57 13 cholesterol, LDL cholesterol, which is bad cholesterol,
08:54:02 14 apolipoprotein B, as well as triglycerides.

08:54:06 15 MR. REIG-PLESSIS: Your Honor, we move the
08:54:07 16 admission of DX 1986 into evidence.

08:54:10 17 MS. KEANE: No objection.

08:54:11 18 THE COURT: DX 1986 is admitted.

08:54:11 19 (Defendants' Exhibit 1986 received in
08:54:16 20 evidence.)

08:54:16 20 BY MR. REIG-PLESSIS:

08:54:17 21 Q So turning to DDX 4.47, there's snapshot of DX 2256,
08:54:22 22 page 2, which is the dosage and administration section of
08:54:26 23 defendants' labels that we reviewed earlier.

08:54:29 24 Does this section mention anything about controlling
08:54:32 25 LDL-C or apo B levels?

08:54:35 1 A It does not. The dosage and administration section
08:54:38 2 specifically gives instruction towards the indication, which
08:54:42 3 is assess lipid levels and identify other causes of high
08:54:48 4 triglyceride levels.

08:54:48 5 Q Does the dosage and administration section mention
08:54:52 6 anything about reducing those high triglyceride levels by any
08:54:56 7 minimum percentage?

08:55:01 8 A It does not.

08:55:03 9 Q Turning to DDX 4.48, there's snapshot of DX 2256, pages 7
08:55:10 10 and 8 from the clinical study section of defendants' labels.

08:55:15 11 First of all, when you prescribe Vascepa, do you
08:55:18 12 expect that the effects described in this section in table 2
08:55:21 13 will necessarily occur in an individual patient?

08:55:24 14 A No, I do not. I understand that each patient responds as
08:55:27 15 an individual to everything that we do for that patient,
08:55:31 16 including medications, certain lifestyle interventions.

08:55:35 17 This tells me, this chart from the MARINE data tells
08:55:38 18 me what could happen.

08:55:41 19 Q So do median data predict what will occur in a given
08:55:45 20 patient?

08:55:46 21 A Median data do not predict. Median data simply, in this
08:55:50 22 example, gives me the median data that would have occurred
08:55:54 23 during this study.

08:55:55 24 For example, there was a median triglyceride
08:55:57 25 reduction, if you look at the first line, of 33 percent. If

08:56:02 1 you go to the second line in which LDL is highlighted, you can
08:56:06 2 see there is a median reduction of two percent.

08:56:09 3 However, if you look through the confidence
08:56:13 4 interval, there are some individuals who actually had an
08:56:17 5 elevation of LDL.

08:56:19 6 If you go to down to the bottom line where it's
08:56:27 7 highlighted for apolipoprotein B, you can see that there was a
08:56:32 8 9 percent reduction for median. However, you can look through
08:56:36 9 the confidence interval and see some individuals had a 3
08:56:40 10 percent reduction.

08:56:41 11 So the answer to your question, this database, this
08:56:44 12 table tells me what transpired during the study. It tells me
08:56:50 13 what could happen. It gives me some ranges of what could
08:56:53 14 happen, but it certainly does not tell me what to expect as I
08:56:57 15 treat an individual patient.

08:57:00 16 Q Now, do you use Vascepa to reduce apo B levels?

08:57:06 17 A I do not. It is not indicated for apo B level reduction.
08:57:10 18 Also, if one were to use this medication specifically for
08:57:14 19 apo B reduction and ignore other medications which are
08:57:19 20 specifically indicated for apolipoprotein B reduction, I would
08:57:23 21 consider that a breach of the standard of care.

08:57:25 22 Q And is the apo B reduction in this study cited here
08:57:31 23 clinically significant in your view?

08:57:32 24 A Well, it's statistically significant in the mean, but it
08:57:37 25 is absolutely not clinically significant.

08:57:39 1 Q Now, did you hear Dr. Budoff compare the clinical study
08:57:45 2 section of the Vascepa label in defendants' products labels to
08:57:51 3 the corresponding section of the Lovaza label?

08:57:54 4 A Yes, I did.

08:57:54 5 Q Is there anything in defendants' labels that refers to
08:57:58 6 Lovaza or the Lovaza label?

08:58:00 7 A There is nothing in the defendants' label that makes
08:58:03 8 reference to Lovaza. In fact, in the defendants' label, in
08:58:10 9 section 6.1, it does specifically tell us that reading
08:58:16 10 physicians cannot realistically refer to a separate study and
08:58:22 11 use that separate study in comparison because the separate
08:58:27 12 studies are potentially using different patient populations,
08:58:31 13 the studies have different designs, and it is advised that we
08:58:34 14 do not look at different studies in a comparative form.

08:58:37 15 Q So is there anything in the clinical study section of
08:58:41 16 defendants' products labels that encourages, recommends, or
08:58:45 17 promotes using defendants' products to achieve the claim lipid
08:58:49 18 effects?

08:58:50 19 A Absolutely not, there's nothing to suggest that.

08:58:52 20 Q And taking now defendants' labels as a whole, do the
08:58:56 21 labels encourage, recommend, or promote administering
08:58:59 22 defendants' products to achieve any minimum triglyceride
08:59:02 23 reduction?

08:59:03 24 A No, sir, they do not.

08:59:04 25 Q Do they encourage, recommend, or promote administering

08:59:08 1 defendants' products to avoid raising LDL-C?

08:59:11 2 A They do not.

08:59:12 3 Q And do they encourage, recommend, or promote
08:59:16 4 administering defendants' products to reduce apo B?

08:59:20 5 A No, they do not.

08:59:22 6 Q What is the next limitation in the asserted claims that
08:59:25 7 you analyzed?

08:59:26 8 A The next analysis that I did was regarding the concurrent
08:59:32 9 lipid-altering therapy limitation.

08:59:35 10 Q So turning to DDX 4.51. What are the asserted claims
08:59:40 11 that exclude concurrent lipid-altering therapy?

08:59:43 12 A So in '728, patent claims 1 and 16, and '715, patent
08:59:50 13 claim 14, it's described as a method of reducing triglycerides
08:59:54 14 in a subject who does not receive concurrent lipid-altering
08:59:59 15 therapy.

08:59:59 16 Q Are statins concurrent lipid-altering therapies?

09:00:03 17 A Yes, sir, they are. It's one of many.

09:00:05 18 Q So are there lipid-altering therapies other than statins?

09:00:10 19 A There are. There is a medicine which is known as Zetia
09:00:15 20 or Ezetimibe that are cholesterol binding resins. There are
09:00:18 21 all sorts of other medications.

09:00:20 22 Q So turning to DDX 4.52, there's a snapshot of DX 2256,
09:00:26 23 page 1. Does the indications and usage section of defendants'
09:00:31 24 products encourage, recommend, or promote excluding concurrent
09:00:36 25 lipid-altering therapy?

09:00:37 1 A It does not. Again, the indication and usage section
09:00:42 2 simply tells us the target population for which this product
09:00:46 3 should be used, which is in adults with severe
09:00:51 4 hypertriglyceridemia as an adjunct to diet.

09:00:57 5 Q And turning to DDX 4.53, with a snapshot of DX 2256,
09:01:05 6 page 2, does the dosage and administration section of
09:01:09 7 defendants' labels encourage, recommend, or promote excluding
09:01:14 8 concurrent lipid-altering therapy?

09:01:16 9 A It absolutely does not.

09:01:25 10 Q Turning to DDX 4.54, there's another snapshot from the
09:01:30 11 same exhibit, DX 2256, now at pages 6 and 7.

09:01:33 12 Are any concurrent lipid-altering therapies
09:01:36 13 described in defendants' labels?

09:01:38 14 A Yes, sir, they are.

09:01:39 15 In the clinical pharmacology section under
09:01:48 16 subsection 12.3 which is the pharmacokinetic section, it
09:01:51 17 describes the use of atorvastatin in this population. So
09:01:54 18 atorvastatin is Lipitor which we just described. It's a drug
09:01:57 19 drug interaction study of 26 healthy adult subjects.

09:02:01 20 And what this tells me is in this small subset it
09:02:05 21 was actually tolerable and there was no significant drug drug
09:02:09 22 interactions with this altering -- with this concurrent
09:02:14 23 lipid-altering therapy.

09:02:16 24 Q So does this statement in the clinical pharmacology
09:02:19 25 section encourage, recommend, or promote excluding concurrent

lipid-altering therapy?

A It does not. In fact, by reading this I can comfortably say that I know this medication can be used with atorvastatin safely.

Q So turning to DDX 4.55, which is page DX 2256, page 7, is there any other statement in defendants' products labels that describes any concurrent lipid-altering therapies?

A Yes, in the clinical study section under severe hypertriglyceridemia, which is subsection 14.2 in which the MARINE trial is described, it goes on to describe, if you look at the highlighted section, that 25 percent of patients were on concomitant statin therapy during the course of the trial.

Q And do defendants' labels indicate whether the remaining 75 percent of patients were on any lipid-altering therapies other than a statin?

A It does not. It's completely silent in that regard.

Q So taking defendants' labels as a whole, do the labels encourage, recommend, or promote administering defendants' products to a patient who does not receive concurrent lipid-altering therapy?

A No, they do not.

Q Do the labels express any preference either way on whether patients should receive such therapy?

A The labels are completely silent in this regard, which leaves this to the discretion of the prescribing physician.

09:03:56 1 Q So turning to DDX 4.57, could you summarize your opinions
09:04:01 2 that you've given over the course of yesterday's testimony and
09:04:05 3 this morning.

09:04:05 4 A Yes, I can.

09:04:07 5 The summary essentially is that the defendants'
09:04:11 6 labels do not encourage, recommend, or promote the claim
09:04:15 7 limitation that require at least 12 weeks of drug treatment,
09:04:19 8 and that was seen in all ten claims that I described.

09:04:22 9 The claim limitations that require specific lipid
09:04:28 10 effects, which, as we described, was triglyceride reduction by
09:04:32 11 a specific percentage, a neutral effect in LDL cholesterol,
09:04:37 12 and a reduction in apolipoprotein B is in nine claims.

09:04:41 13 And it does not recommend, promote, or encourage the
09:04:44 14 limitations that require excluding concurrent lipid-altering
09:04:47 15 therapy, and that was in the last three claims that we just
09:04:51 16 described.

09:04:52 17 MR. REIG-PLESSIS: Thank you, Dr. Sheinberg. I
09:04:54 18 have no further questions at this time.

09:05:07 19 MS. KEANE: Good morning, Your Honor. May we
09:05:09 20 approach with a binder for Dr. Sheinberg?

09:05:13 21 THE COURT: Yes.

09:05:13 22 MS. KEANE: Thank you.

09:05:37 23 CROSS-EXAMINATION

09:05:37 24 BY MS. KEANE:

09:05:38 25 Q Good morning, Dr. Sheinberg. I know we've met before at

09:05:40 1 your deposition. I'm Meagan Keane, and I will be asking you
09:05:45 2 some questions on behalf of the plaintiffs.

09:05:46 3 A Good morning.

09:05:47 4 Q Good morning.

09:05:48 5 I just want to start off with a housekeeping issue.
09:05:51 6 You discussed the Vascepa label as well as defendants' labels
09:05:54 7 during your direct testimony, and I just want to make clear
09:05:57 8 that for purposes of my questions we can -- if questions
09:06:00 9 pertain to one label, then they pertain equally to the other
09:06:05 10 labels as well.

09:06:06 11 A Understood.

09:06:07 12 Q Okay. So first I want to ask you a few questions about
09:06:10 13 the analysis that you conducted in order to reach your
09:06:14 14 opinions in this case.

09:06:16 15 So to determine whether the labels, defendants'
09:06:20 16 labels in this case, will induce infringement, it was your
09:06:24 17 understanding that the label must contain a specific
09:06:26 18 instruction in order for the prescriber, this prescribing
09:06:31 19 label to recommend, encourage, or promote; is that correct?

09:06:34 20 A Yes.

09:06:34 21 Q Okay. And you would agree with me that doctors who are
09:06:39 22 reading prescribing information, they go through years of
09:06:42 23 schooling and years of training.

09:06:43 24 A Yes, that's correct.

09:06:44 25 Q In medical school, internships, residencies, fellowships.

09:06:49 1 A Yes.

09:06:49 2 Q And so when a physician is reading a label, they can't
09:06:53 3 eliminate all of that education and all that training.

09:06:56 4 A Of course not.

09:06:57 5 Q They use their background knowledge when reading
09:07:00 6 prescribing information.

09:07:01 7 A Yes, I should hope so.

09:07:07 8 Q And, now, my understanding as well is that your view is
09:07:10 9 that there are only a few sections of the labeling that can
09:07:14 10 actually instruct a physician on how to use a drug with
09:07:18 11 respect to the analysis in that case; is that right?

09:07:20 12 A No, that's not correct.

09:07:21 13 Q Okay. And specifically, does the sections of the label
09:07:26 14 that, in your understanding, can instruct a physician with
09:07:29 15 respect to how to use a drug, are the indications and usage
09:07:33 16 section, the dosage and administration section, and the
09:07:36 17 contraindication section; is that correct?

09:07:38 18 A Those are the most likely areas in which the instructions
09:07:43 19 would be found, but the label should be taken in its entirety.

09:07:48 20 Q And with respect to -- with respect to your analysis,
09:07:53 21 those are the three -- those are the three sections in the
09:07:55 22 labeling that you understood to be able to instruct an
09:07:59 23 infringement with respect to an inducement analysis.

09:08:02 24 A Most often I would say yes, but I would have to qualify
09:08:06 25 that by saying the rest of the label cannot be completely

09:08:09 1 ignored at the same time. It needs to be looked at in its
09:08:13 2 entirety.

09:08:14 3 MS. KEANE: Okay. Mr. Brooks, if you could
09:08:16 4 play --

09:08:16 5 BY MS. KEANE:

09:08:17 6 Q Actually, Dr. Sheinberg, you were deposed in this case,
09:08:20 7 correct?

09:08:20 8 A Yes, I was.

09:08:20 9 Q And you were under oath at the time?

09:08:22 10 A Yes, I was.

09:08:23 11 MS. KEANE: Mr. Brooks, could we play 120, 16 to
09:08:26 12 21.

09:08:28 13 (Video deposition playing.)

09:08:46 14 BY MS. KEANE:

09:08:57 15 Q And, Dr. Sheinberg, your understanding --

09:08:58 16 MR. REIG-PLESSIS: Your Honor, I object. That's
09:09:01 17 not proper impeachment. The question was what sections can
09:09:05 18 instruct a physician. I think that's consistent with his
09:09:12 19 testimony that those are sections that can instruct a
09:09:14 20 physician.

09:09:15 21 THE COURT: Ms. Keane?

09:09:16 22 MS. KEANE: Your Honor, I disagree with Dr. --
09:09:23 23 or Mr. Reig's characterization. I think it is proper
09:09:26 24 impeachment testimony. At the time of the question, it's
09:09:31 25 clear that Dr. Sheinberg was referring to only those three

09:09:34 1 sections of the labeling.

09:09:35 2 THE COURT: Well, his -- I assume the point of
09:09:39 3 the impeachment was to point out that previously he identified
09:09:44 4 three areas that one look at to determine inducement.

09:09:51 5 It's a close call. I'm going to overrule the
09:09:53 6 objection. The testimony is already in. I'll give it
09:09:55 7 whatever weight I think it deserves.

09:09:58 8 MS. KEANE: Thank you, your Honor.

09:09:59 9 BY MS. KEANE:

09:10:00 10 Q Dr. Sheinberg, your understanding of which sections of
09:10:02 11 the label can specifically instruct a physician, that opinion
09:10:06 12 is informed by an expert report submitted in this case by Mr.
09:10:09 13 Mathers; is that correct?

09:10:11 14 A That was a contributory -- that contributed to it, yes.

09:10:16 15 Q Okay. And Mr. Mathers -- he submitted a report --
09:10:20 16 Mr. Mathers' purports to be regulatory expert in this case; is
09:10:25 17 that correct?

09:10:25 18 A Yes.

09:10:25 19 Q And you reviewed Mr. Mathers' report in preparing your
09:10:29 20 report in this case?

09:10:30 21 A Yes.

09:10:30 22 Q And in forming your opinions in this case?

09:10:32 23 A Yes.

09:10:32 24 Q And, in fact, you relied extensively on Mr. Mathers'
09:10:36 25 report throughout your report in this case?

09:10:38 1 A I wouldn't say extends -- yes, I relied on it.

09:10:42 2 Q And, in fact, you cited Mr. Mathers' report 14 times in
09:10:46 3 your expert report?

09:10:48 4 A I will take your word for that, yes.

09:10:49 5 Q And you would agree with me you're not an expert on FDA
09:10:54 6 procedures?

09:10:54 7 A No, ma'am, I am not.

09:10:56 8 Q Okay. And your understanding of the FDA's approval
09:10:59 9 process is minimal?

09:11:00 10 A That is correct.

09:11:01 11 Q And the minimal understanding that you do have, that's
09:11:03 12 based on Mr. Mathers' expert report?

09:11:06 13 A I would imagine most of it would probably be based on
09:11:11 14 what I read in Mr. Mathers' report.

09:11:17 15 Q Just to be clear, for purposes of your opinions in this
09:11:20 16 case, you did not review FDA guidance?

09:11:23 17 A I did not.

09:11:24 18 Q You did not review the U.S. Code of Federal Regulations?

09:11:27 19 A No, ma'am.

09:11:28 20 Q And even though you cited both FDA guidance and U.S. Code
09:11:34 21 of Federal Regulations in your expert report?

09:11:37 22 A I would imagine I cited those on behalf of reading what I
09:11:40 23 read in Mr. Mathers' testimony or his report.

09:11:43 24 Q Because you agree with me that you cited both of those
09:11:46 25 documents in your report?

09:11:47 1 A I'd have to have the document in front of me, but I have
09:11:50 2 no reason to not believe what you're saying.

09:11:52 3 MS. KEANE: Okay. Mr. Brooks, if we could pull
09:11:56 4 up Mr. Sheinberg's -- or Dr. Sheinberg's report, it's DX 1697,
09:12:09 5 paragraph 64.

09:12:09 6 BY MS. KEANE:

09:12:21 7 Q Okay. And, Dr. Sheinberg, you see paragraph 64 from your
09:12:24 8 expert report?

09:12:25 9 A Yes.

09:12:25 10 Q And you agree with me that you cited in paragraph 64 the
09:12:30 11 CFR, which is the U.S. Code of Federal Regulations?

09:12:40 12 A Yes.

09:12:45 13 MS. KEANE: Mr. Brooks, if we could turn to
09:12:47 14 paragraph 80.

09:12:47 15 BY MS. KEANE:

09:12:53 16 Q And, Dr. Sheinberg, you see in paragraph 80 that you
09:12:56 17 cited FDA clinical studies guidance?

09:13:00 18 A Yes. Would you give me just a moment so I may read this?

09:13:03 19 Q Sure.

09:13:04 20 A (Witness reviews document.)

09:13:30 21 Yes, that is correct.

09:13:32 22 Q Earlier during your direct testimony this morning you
09:13:37 23 discussed testimony from this case from Dr. Carl Peck. Do you
09:13:41 24 recall that?

09:13:41 25 A Yes, I do.

09:13:43 1 Q Do you have an understanding that Dr. Peck is a
09:13:45 2 regulatory expert?

09:13:46 3 A I do.

09:13:47 4 Q And as we discussed today, you're not a regulatory
09:13:49 5 expert.

09:13:50 6 A No, ma'am, I am not.

09:13:51 7 Q And I want to go back to your analysis in this case.

09:14:12 8 Is it your understanding with respect to the labels
09:14:15 9 in this case that some physicians could read the label and be
09:14:20 10 induced to infringe?

09:14:21 11 A It is -- can you repeat -- please say that one more time
09:14:21 12 for me, please?

09:14:25 13 Q Is it possible that some physicians could read the label,
09:14:28 14 the labels, and be induced to infringe?

09:14:32 15 A I think anything is potentially possible.

09:14:38 16 Q And so you would agree with me that in this case that's
09:14:42 17 possible?

09:14:42 18 MR. REIG-PLESSIS: Objection. If the question
09:14:44 19 is if something is possible, I would object as calling for
09:14:49 20 speculation.

09:14:49 21 THE COURT: The objection is overruled. The
09:14:50 22 question is already answered, she's just reiterating his
09:14:53 23 question.

09:14:56 24 Would you repeat the question.

09:14:58 25 BY MS. KEANE:

09:14:58 1 Q Sure. My question is just it's possible.

09:15:00 2 A Yes, I think anything is possible.

09:15:06 3 MS. KEANE: Okay. If we could turn to trial
09:15:12 4 Exhibit 1186, and if we could turn to the second page,
09:15:19 5 Mr. Brooks, and pull up the indications and usage section. If
09:15:25 6 we could highlight the second indication.

09:15:25 7 BY MS. KEANE:

09:15:36 8 Q And, Dr. Sheinberg, that indication is as an adjunct to
09:15:39 9 diet to reduce triglyceride levels in adult patients with
09:15:43 10 severe, greater than 500 milligrams per deciliter,
09:15:47 11 hypertriglyceridemia, do you see that?

09:15:48 12 A Yes, I do.

09:15:49 13 Q The indications and usage section in the prescribing
09:15:53 14 information is a section that instructs a clinician about when
09:15:55 15 to use a drug, correct?

09:15:57 16 A Correct.

09:15:58 17 Q Okay. And so do you agree with me that this statement in
09:16:01 18 the indications and usage section encourages doctors to
09:16:05 19 administer Vascepa to patients to reduce triglyceride levels
09:16:09 20 in subjects having fasting baseline triglyceride levels of
09:16:13 21 500 milligrams per deciliter or higher?

09:16:15 22 A As an adjunct to diet, yes.

09:16:18 23 Q If we could turn to section 2.2 of the labeling, and
09:16:33 24 under the dosage and administration section, the first bullet
09:16:38 25 says the daily dose of Vascepa is 4 grams per day, do you see

09:16:43 1 that?

09:16:43 2 A Yes, I do.

09:16:43 3 Q And the administration -- the dosage and administration
09:16:47 4 section is another section that could instruct physicians?

09:16:51 5 A Yes.

09:16:51 6 Q And you would agree that the statement in the dosage and
09:16:54 7 administration section instructs clinicians to administer 4
09:16:59 8 grams per day of Vascepa in patients with severe
09:17:02 9 hypertriglyceridemia?

09:17:02 10 A Yes.

09:17:03 11 Q And if we take a look at the last bullet point in that
09:17:08 12 section, advise patients to swallow Vascepa capsules whole, do
09:17:13 13 you see that?

09:17:13 14 A Yes.

09:17:13 15 Q You would agree with me that the dosage and
09:17:16 16 administration section instructs clinicians that the -- I'm
09:17:22 17 sorry, let me rephrase the question.

09:17:23 18 You agree that the statement in the dosage and
09:17:27 19 administration section instructs clinicians to administer
09:17:30 20 Vascepa orally?

09:17:31 21 A Yes.

09:17:34 22 Q I just want to talk about a couple of your prescribing
09:17:41 23 practices.

09:17:42 24 A Okay.

09:17:43 25 MS. KEANE: Mr. Brooks, we can take down the

09:17:44 1 label.

09:17:44 2 BY MS. KEANE:

09:17:46 3 Q So typically when lipids are measured it's after a
09:17:50 4 12-hour fast; is that right?

09:17:51 5 A Typically, yes.

09:17:52 6 Q And when you determine your patient's lipid levels, you
09:17:56 7 use an advanced lipid panel?

09:17:59 8 A I do.

09:17:59 9 Q An advanced lipid panel differs from a standard lipid
09:18:04 10 panel?

09:18:04 11 A Yes, it does.

09:18:05 12 Q The advanced lipid panel includes additional biomarkers
09:18:10 13 that are not in the standard lipid panel?

09:18:12 14 A Correct.

09:18:12 15 Q For example, apo B?

09:18:15 16 A Yes.

09:18:15 17 Q And apo B is a biomarker that you use in your clinical
09:18:20 18 practice.

09:18:20 19 A Correct.

09:18:20 20 Q And apo B is a biomarker that you consider very important
09:18:20 21 to your clinical practice.

09:18:24 22 A Correct.

09:18:25 23 Q So when you treat patients with severe
09:18:30 24 hypertriglyceridemia, you use a stepwise approach; is that
09:18:40 25 crept?

09:18:40 1 A When you say stepwise approach, can you be more specific?

09:18:44 2 It really varies from patient to patient.

09:18:47 3 Q Okay. It's -- what is your understanding of what a
09:18:49 4 stepwise approach is?

09:18:50 5 A Well, my understanding is you do one step first and then
09:18:54 6 a second step and then a third step.

09:18:56 7 But when I treat patients, a stepwise approach, it's
09:19:00 8 not a -- when I treat patients, a stepwise approach implies
09:19:05 9 that every patient will receive the same steps in every single
09:19:10 10 order and that's not the case.

09:19:11 11 Q So with respect to severe hypertriglyceridemia, there are
09:19:19 12 four -- four different drugs that are approved to treat severe
09:19:25 13 hypertriglyceridemia; is that right?

09:19:26 14 A Yes.

09:19:28 15 Q And one of those -- well, clinicians who are treating
09:19:32 16 patients with severe hypertriglyceridemia, they would be
09:19:35 17 familiar with those agents?

09:19:36 18 A They should be.

09:19:37 19 Q And one of those agents is niacin?

09:19:40 20 A Yes.

09:19:40 21 Q And you would agree with me that niacin is not a good
09:19:43 22 medication for anybody?

09:19:45 23 A I would not agree with that statement.

09:19:47 24 Q Would you agree with me that niacin is not a great
09:19:57 25 medication for anybody?

09:20:00 1 THE COURT: I'm sorry, was that the same
09:20:01 2 question?

09:20:03 3 MS. KEANE: It's a slightly different question.

09:20:04 4 THE COURT: What's the question again?

09:20:05 5 BY MS. KEANE:

09:20:06 6 Q Would agree with me that niacin is not a great medication
09:20:09 7 for anybody?

09:20:09 8 A I would not use the absolute terms. There are certain
09:20:14 9 people that niacin would still benefit from, although the
09:20:19 10 population is very limited at this point.

09:20:21 11 Q Let's talk about fibrates. Fibrates are -- in your
09:20:25 12 practice are a second-line therapy?

09:20:27 13 A Again, it's really individually determined by the patient
09:20:30 14 and what's going on. But frequently, yes, they are a second-
09:20:34 15 or third-line therapy.

09:20:36 16 Q And to be specific, with respect to patients with severe
09:20:38 17 hypertriglyceridemia.

09:20:40 18 A Correct.

09:20:44 19 Q And one of the reasons that fibrates are not a first-line
09:20:51 20 therapy for you is because of the side effects and drug drug
09:20:54 21 interactions associated with fibrates?

09:20:56 22 A Correct.

09:20:57 23 Q And the drug drug interactions associated with fibrates
09:21:03 24 those are interactions in conjunction with statins?

09:21:06 25 A Yes, ma'am.

09:21:07 1 Q And when administered together, fibrates and statins, you
09:21:11 2 will see myalgia, muscle pain, and GI upset?

09:21:16 3 A Not -- you can. It's not a 100 percent given that it
09:21:24 4 will happen, but there is a higher risk of that when those
09:21:27 5 medications are used together.

09:21:28 6 Q Those are certainly recognized side effects of fibrates.

09:21:32 7 A Yes, they are.

09:21:33 8 Q And fibrates can also increase LDL-C.

09:21:36 9 A Yes, they can.

09:21:37 10 Q And now let's turn to your first-line therapy for
09:21:41 11 treating patients with severe hypertriglyceridemia.

09:21:43 12 And so your first-line therapy is an omega-3
09:21:48 13 pharmaceutical product.

09:21:51 14 A So when -- did you say severe hypertriglyceridemia or
09:21:56 15 hypertriglyceridemia?

09:21:57 16 Q For treating patients with severe hypertriglyceridemia
09:22:00 17 your first-line therapy is an omega-3 pharmaceutical product.

09:22:05 18 A This is an example where the stepwise plan really doesn't
09:22:10 19 come into complete -- it doesn't come into complete play here
09:22:15 20 because it really is individually patient specific.

09:22:18 21 Oftentimes several medications may be prescribed at
09:22:21 22 the same time. It really depends on the individual patient
09:22:24 23 and their clinical history.

09:22:25 24 Q Certainly your primary therapy for -- drug therapy for
09:22:29 25 treating patients with severe hypertriglyceridemia are

09:22:31 1 omega-3s?

09:22:34 2 A It depends on the patient population. I can give several
09:22:38 3 examples in which a single agent would not be appropriate in
09:22:41 4 that population and in which case a single agent would
09:22:44 5 potentially be appropriate.

09:22:45 6 Q Is it true that you prefer Vascepa to Lovaza?

09:22:52 7 A Yes, it is.

09:22:52 8 Q In your practice you also regularly prescribe statins; is
09:22:56 9 that right?

09:22:56 10 A Yes, I do.

09:22:57 11 Q And prescription of statins is standard of care for
09:23:00 12 patients with cardiovascular risk?

09:23:03 13 A Yes.

09:23:03 14 Q And once statins -- once patients are on a statin, they
09:23:07 15 are potentially on a statin indefinitely.

09:23:10 16 A Yes, I used a term like I mentioned earlier, it's
09:23:12 17 treatment, not a cure.

09:23:16 18 Q And that's true even after patients -- those patients'
09:23:20 19 LDL-C goals drop below a goal level.

09:23:24 20 A Correct.

09:23:25 21 Q And that's because if a patient is taken off a statin,
09:23:29 22 the LDL-C levels will go back up.

09:23:32 23 A Typically they do.

09:23:33 24 Q And the LDL-C levels will go back up because there's
09:23:37 25 underlying genetic issues.

09:23:39 1 A Correct.

09:23:39 2 Q Let's talk a little bit about your prescribing habits.

09:23:46 3 When you prescribe icosapent ethyl, you typically
09:23:50 4 prescribe it with refills as well, correct?

09:23:52 5 A I do.

09:23:53 6 Q And so one option is a prescription for three months with
09:24:00 7 three refills?

09:24:01 8 A Yes.

09:24:02 9 Q For a one year in total?

09:24:04 10 A Yes.

09:24:04 11 Q Or one month with three refills?

09:24:06 12 A Yes.

09:24:07 13 Q For four months in total.

09:24:09 14 A Correct.

09:24:09 15 Q And those are the typical types of -- I'm sorry, let me
09:24:14 16 rephrase the question.

09:24:15 17 Those are the typical durations that you use in
09:24:18 18 prescribing icosapent ethyl.

09:24:19 19 A Yes, it is.

09:24:29 20 Q One the things that we talked about -- well, when you
09:24:35 21 treat your patients, you have specific goals for your
09:24:38 22 patient's lipid levels; is that right?

09:24:40 23 A Yes.

09:24:41 24 Q And typically for patients who aren't meeting their
09:24:45 25 goals, you see them back at three to six-month intervals?

09:24:49 1 A So that's a rather broad statement. I will see them back
09:24:53 2 in a varying amount of time, anywhere between two months, four
09:24:56 3 months, six months, depending on what type of intervention is
09:25:00 4 made, what their calendar and schedule look like, what my
09:25:04 5 calendar looks like, but it varies.

09:25:07 6 Q Three -- would three to six months be typical?

09:25:11 7 A Not necessarily. I would say two, four or six months
09:25:15 8 would be typical.

09:25:16 9 Q And then once your patients have reached goals, you
09:25:19 10 extend those visits out to once a year?

09:25:21 11 A Yes, I do.

09:25:28 12 Q And patients maintain those goals by maintaining their
09:25:36 13 current lifestyle and their current drug therapy.

09:25:39 14 A Yes.

09:25:39 15 Q So let's talk little bit about the labels in this case.

09:25:57 16 Would you agree with me that a prescribing physician
09:26:01 17 who is looking at defendants' labels to understand the amount
09:26:05 18 of time necessary to see the treatment effects for
09:26:08 19 administration of icosapent ethyl would look to the clinical
09:26:12 20 study section?

09:26:13 21 A Can you repeat -- that question had so many different
09:26:17 22 components, would you mind rephrasing it for me, please?

09:26:20 23 Q Okay. Let me try the question again. I'll ask it a
09:26:23 24 little bit slower.

09:26:25 25 A Please.

09:26:25 1 Q A prescribing physician who is looking at the label to
09:26:30 2 understand the amount of time necessary to see the treatment
09:26:33 3 effects from administration of icosapent ethyl would look at
09:26:45 4 the clinical study section.

09:26:47 5 A Yes, but they would look at the label in its entirety,
09:26:51 6 and the clinical study section would simply give them
09:26:52 7 information about the clinical study that was performed but
09:26:53 8 not necessarily the duration of therapy that would be used in
09:26:57 9 their individual patient population.

09:26:58 10 Q And you recall one of the things we discussed in your
09:27:04 11 deposition, that an understanding of the clinical trials for a
09:27:07 12 medication is vital to using that medication.

09:27:11 13 A Yes.

09:27:20 14 MS. KEANE: Mr. Brooks, if you could pull up
09:27:22 15 PDX 3-2.

09:27:22 16 BY MS. KEANE:

09:27:34 17 Q And, Dr. Sheinberg, on the screen on plaintiff's or
09:27:40 18 PDX 3-2 is testimony from Mr. Mathers, do you see that?

09:27:44 19 A Yes, I do.

09:27:45 20 Q Again, this is the same Mr. Mathers who you relied on in
09:27:48 21 your expert report?

09:27:49 22 A Yes.

09:27:49 23 Q And Mr. Mathers was asked during his deposition,

09:27:54 24 "So the goal of the clinical study section is
09:27:57 25 to facilitate a prescriber's understanding of how to

09:28:01 1 use the drug safely and effectively, correct?"

09:28:04 2 And he answered, "That's one of the goals,
09:28:06 3 yes."

09:28:06 4 Do you see that?

09:28:06 5 A Yes.

09:28:07 6 Q Do you agree with that?

09:28:08 7 A Yes, I do.

09:28:11 8 MS. KEANE: Okay. Now, if we could --

09:28:18 9 Mr. Brooks, if we could go to Plaintiffs' Exhibit 1186 and
09:28:28 10 pull up section 14.2.

09:28:28 11 BY MS. KEANE:

09:28:31 12 Q And Plaintiff's 1186, section 14.2, this is the clinical
09:28:36 13 study section of the Vascepa labeling?

09:28:40 14 A Are you asking me -- yes.

09:28:41 15 Q And the clinical study that's summarized there, that's
09:28:48 16 the MARINE study?

09:28:49 17 A Correct.

09:28:49 18 Q And in the clinical study section of the label, the
09:28:53 19 labeling only provides the effect of the drug after 12 weeks?

09:28:57 20 A Correct.

09:28:57 21 Q There's no data in the label for the effects at four
09:29:05 22 weeks.

09:29:05 23 A Not in the label.

09:29:06 24 Q And there's no data in the label with respect to the
09:29:09 25 effects at eight weeks.

09:29:10 1 A There is not.

09:29:11 2 Q And this section that depicts the results or the effects
09:29:15 3 of the drug in 12 weeks, this information is vital to an
09:29:20 4 understanding of how to use the drug.

09:29:23 5 A To quote Mr. Mathers, it certainly facilitates our
09:29:29 6 understanding. It is important.

09:29:30 7 But, as you mentioned earlier, counselor, there
09:29:33 8 are -- we do look at these trials with three years of
09:29:38 9 residency, three years of cardiology fellowship, and multiple
09:29:43 10 years of practice behind us, and those experiences that we
09:29:45 11 have also shed light on how patients respond and how the dose
09:29:51 12 responses vary from individual to individual.

09:29:54 13 Q If we take a look at table 2 in the labeling, in the --
09:30:02 14 with respect to triglyceride levels, the results shown here
09:30:05 15 are 25 percent -- or, I'm sorry, a 27 percent reduction in
09:30:10 16 triglycerides compared to baseline?

09:30:12 17 A Correct.

09:30:12 18 Q And a 27 percent reduction compared to baseline is
09:30:16 19 consistent with your experience using Vascepa.

09:30:18 20 A That is correct.

09:30:19 21 Q And if we could turn next to take a look at LDL-C. And
09:30:30 22 the LDL-C section of the labeling does not report any increase
09:30:35 23 in LDL-C.

09:30:37 24 A That is correct.

09:30:38 25 Q And, in fact, if we take a look at the table below -- or,

09:30:43 1 I'm sorry, the text below the table, there is a statement
09:30:51 2 there that says,

09:30:52 3 "The reduction in TG observed with Vascepa
09:30:55 4 was not associated with elevations in LDL-C levels
09:30:59 5 relative to placebo."

09:31:01 6 Do you see that?

09:31:02 7 A Yes.

09:31:02 8 Q And so prescribers looking at the labeling will
09:31:06 9 understand that the labeling is telling them that they can
09:31:08 10 administer Vascepa to their severe hypertriglyceridemic
09:31:12 11 patients so as to reduce triglycerides without raising LDL-C;
09:31:17 12 is that correct?

09:31:17 13 A Again, the answer to your question is no, not
09:31:20 14 necessarily. It will simply describe what was seen in this
09:31:24 15 trial, and it is my hope that individuals who read this would
09:31:27 16 read across the line and realize that there is -- even though
09:31:31 17 there was a reduction, some individuals had an actual increase
09:31:36 18 in their LDL-C.

09:31:37 19 So I would believe that a physician who reads this
09:31:41 20 would read the entire document and the entire line and
09:31:44 21 understand that was the response that was seen in the trial.
09:31:47 22 However, individual responses may vary.

09:31:50 23 MS. KEANE: Okay. Mr. Brooks, could we pull up
09:31:54 24 PDX 3-3.

09:31:54 25 BY MS. KEANE:

09:32:00 1 Q Dr. Sheinberg, do you see PDX 3-3 includes testimony
09:32:05 2 again from Mr. Mathers?

09:32:07 3 A Yes, I do.

09:32:08 4 Q And do you see in PDX 3-3 Mr. Mathers was asked,
09:32:14 5 "Some prescribers will understand the Vascepa
09:32:17 6 labeling to tell them that they can administer
09:32:20 7 Vascepa to their severely hypertriglyceridemic
09:32:22 8 patients so as to reduce the triglyceride levels
09:32:26 9 without raising LDL-C, correct?"

09:32:28 10 And then he responded, "I think that's a
09:32:31 11 fair prediction."

09:32:32 12 A I do see that.

09:32:34 13 Q Okay. And do you agree with Mr. Mathers?

09:32:41 14 A Yes. However, I cannot really speculate at what some
09:32:47 15 prescribers would do. I can only speculate as to what I would
09:32:51 16 do and what some of the experienced colleagues I work with
09:32:54 17 would do.

09:32:55 18 But, yes, I'm sure some people would read this label
09:32:59 19 and presume one thing, and others would read the label and
09:33:02 20 presume something else.

09:33:11 21 Q During your direct examination you relied on the -- one
09:33:19 22 of the things that you discuss was the MARINE clinical study
09:33:22 23 report; is that right?

09:33:23 24 A Yes, that is.

09:33:24 25 MS. KEANE: If we could pull up DDX 4.26.

09:33:24 1 BY MS. KEANE:

09:33:35 2 Q And you noted that there's some data relating to LDL-C in
09:33:38 3 the MARINE clinical study report?

09:33:41 4 A Correct.

09:33:41 5 Q And you agree with me that that information is not in the
09:33:44 6 labeling.

09:33:45 7 A That is not in the labeling.

09:33:46 8 Q And that document is not even publically available.

09:33:49 9 A That is correct.

09:33:50 10 Q And that's information that you had access to solely for
09:33:54 11 purposes of your involvement in this case.

09:33:55 12 A Correct.

09:33:56 13 Q Dr. Sheinberg, I think you were asked by counsel this
09:34:09 14 morning whether or not the Lovaza -- Lovaza's effects on LDL-C
09:34:18 15 are referenced in -- in the labeling. Do you recall that?

09:34:25 16 A In whose labeling?

09:34:27 17 Q In defendants' labeling.

09:34:29 18 A Yes, I do recall that.

09:34:42 19 MS. KEANE: And if we could go to Plaintiffs'
09:34:57 20 Exhibit 289.

09:34:57 21 BY MS. KEANE:

09:35:01 22 Q So Plaintiffs' Exhibit 289 is the medical review for
09:35:04 23 Vascepa. Do you see that?

09:35:09 24 A Yes, I do.

09:35:10 25 Q And is this a document you're familiar with?

09:35:12 1 A Yes, it is.

09:35:13 2 Q And the medical review reflects important background
09:35:18 3 information that a person of ordinary skill in the art would
09:35:21 4 understand and bring to bear when using defendants' ANDA
09:35:27 5 products as indicated?

09:35:29 6 A Correct.

09:35:30 7 Q And if we could turn to page 14 of the medical review.
09:35:41 8 If you see in section 2.4, section 2.4 of the labeling does
09:35:50 9 refer to Lovaza, correct -- I'm sorry, section 2.4 of the
09:35:53 10 medical review does refer to Lovaza, correct?

09:35:56 11 A If you give me a moment to read, this I'll be able to
09:36:00 12 answer your question.

09:36:02 13 (Witness reviews document.)

09:36:14 14 That is correct.

09:36:15 15 Q And section 2.4 of the medical review states,

09:36:18 16 "With regard to the only other FDA approved
09:36:21 17 Omega 3 fatty acid product (Lovaza), there have been
09:36:27 18 four areas of potential safety concern."

09:36:29 19 And the first one listed is increases in LDL-C.
09:36:32 20 Do you see that?

09:36:33 21 A Yes.

09:36:33 22 Q Okay. So you would agree with me that that information
09:36:35 23 is important background information that a person of ordinary
09:36:39 24 skill in the art would understand and bring to bear when using
09:36:42 25 defendants' ANDA products as indicated?

09:36:45 1 A Yes.

09:36:45 2 Q And you would agree with me that physicians would look to
09:36:56 3 the FDA medical review to understand defendants' labels?

09:37:00 4 A Not necessarily.

09:37:03 5 Q And for purposes of your analysis in the case, you
09:37:18 6 understand the medical review to contain important background
09:37:22 7 information that would inform physicians' understanding of
09:37:25 8 what to bring to bear to use the defendants' ANDA product in
09:37:29 9 the case.

09:37:29 10 A Correct.

09:37:29 11 Q So I just want to be clear on one thing. To be clear,
09:37:41 12 you do not typically prescribe Vascepa for short-term
09:37:45 13 treatment.

09:37:45 14 A No, I typically prescribe Vascepa long term.

09:37:49 15 Q And, in your experience, that's consistent with other
09:37:53 16 physicians as well.

09:37:54 17 A Yes, it is.

09:37:54 18 Q Like Dr. Budoff.

09:37:57 19 A Yes, it is.

09:37:57 20 Q And when you treat patients with severe
09:38:00 21 hypertriglyceridemia, your goal is to both reduce and maintain
09:38:05 22 triglyceride levels; is that right?

09:38:07 23 A That is correct.

09:38:09 24 Q And that is standard practice.

09:38:11 25 A Yes.

09:38:12 1 Q Another area where your practice is consistent with
09:38:18 2 Dr. Budoff's.

09:38:20 3 A Correct, although I use Vascepa most often long-term, not
09:38:25 4 for its triglyceride-lowering effect but for the other
09:38:29 5 benefits that I have already mentioned.

09:38:31 6 So I think even though Dr. Budoff and I will use the
09:38:34 7 product for extended periods of time, the rationale between
09:38:39 8 the way I use it and the rationale between the way he uses it
09:38:42 9 is rather different.

09:38:43 10 Q And, Dr. Sheinberg, that -- that's was -- for my
09:38:45 11 question, my question was really just that you would agree
09:38:48 12 that when you treat patients with severe hypertriglyceridemia
09:38:51 13 the goal is both to reduce and maintain triglyceride levels.

09:38:56 14 A I thought that's how I answered the question, so not
09:39:00 15 necessarily. I do not use the medication to maintain
09:39:03 16 triglyceride levels. I use the medication for the other
09:39:07 17 beneficial effects seen on the inflammatory markers and the
09:39:11 18 lipid parameters like I had mentioned.

09:39:13 19 Q Okay. So let me just be clear. My question is not with
09:39:16 20 respect to a particular medication.

09:39:18 21 A Right.

09:39:18 22 Q My question for you is just simply in medical practice
09:39:21 23 the goal for triglyceride reduction with patients -- in
09:39:23 24 patients with severe hypertriglyceridemia is to both reduce
09:39:27 25 triglycerides and maintain that reduction.

09:39:31 1 A Correct.

09:39:31 2 Q And that reduction and maintenance, that's consistent
09:39:35 3 with what other physicians would do.

09:39:37 4 A Correct.

09:39:39 5 Q And in order for patients to maintain those triglyceride
09:39:43 6 reductions, patients need to continue with therapy.

09:39:47 7 A By therapy, can you be more specific so I can answer your
09:39:52 8 question appropriately?

09:39:53 9 Q Well, the patients need to continue with the therapy that
09:39:58 10 they've engaged in with their physician to keep the
09:40:01 11 triglyceride reductions maintained.

09:40:03 12 A If by therapy you mean lifestyle modifications as well,
09:40:07 13 then, yes, I agree with that statement.

09:40:09 14 Q And they have to do that because the underlying
09:40:13 15 mechanisms for severe hypertriglyceridemia are chronic.

09:40:18 16 A That's not true.

09:40:20 17 Q And so when -- you would agree with me that when therapy
09:40:25 18 is removed from patients with severe hypertriglyceridemia,
09:40:28 19 they -- the triglycerides will potentially increase again.

09:40:32 20 A So, again, in order to answer your question the best way
09:40:38 21 I can, I need have a better definition of how you're
09:40:41 22 describing the word therapy.

09:40:43 23 As I hear your question, therapy may mean lifestyle
09:40:46 24 modifications, and, if so, if the lifestyle modifications
09:40:49 25 which are the underlying problem are, in one hand, fixed, and

09:40:53 1 then they revert back to the pretreatment way, then, yes, I
09:40:57 2 think the problem will recur.

09:40:59 3 Q If we could turn to -- well, Dr. Sheinberg one of the
09:41:11 4 documents that you referred to during your direct examination
09:41:13 5 was the ATP III.

09:41:15 6 A Yes.

09:41:16 7 Q And that is, I believe, DX 1876.

09:41:21 8 Would you agree with me that the ATP III also
09:41:25 9 reflects important background information that a POSA would
09:41:31 10 understand and bring to bear in using Vascepa or defendants'
09:41:37 11 ANDA products for their indicated use of reducing
09:41:37 12 triglycerides in patients with triglycerides of at least 500
09:41:39 13 milligrams per deciliter?

09:41:41 14 A Yes.

09:42:00 15 MS. KEANE: If we could take a look at DDX 4.10.

09:42:00 16 BY MS. KEANE:

09:42:09 17 Q Okay. Dr. Sheinberg, on DDX 4.10, you have a call-out on
09:42:17 18 this slide from ATP III?

09:42:20 19 A Yes.

09:42:20 20 Q ATP III is quite a lengthy document; is that right?

09:42:24 21 A It is.

09:42:25 22 Q Okay. And so on this slide you pulled out one sentence
09:42:28 23 from ATP III.

09:42:29 24 A Correct.

09:42:30 25 Q And then if -- and then in your testimony you moved to

09:42:34 1 DDX 4.11.

09:42:38 2 MS. KEANE: So, Mr. Brooks, can we pull that up?

09:42:38 3 BY MS. KEANE:

09:42:40 4 Q Which is the Amarin website.

09:42:41 5 A Correct.

09:42:41 6 Q And you used the Amarin website in your discussion of
09:42:47 7 what you believe are the causes of severe
09:42:49 8 hypertriglyceridemia?

09:42:50 9 A Yes.

09:42:51 10 MS. KEANE: Okay. Well, let's take a look back
09:42:53 11 at the ATP III. Okay. Now, the -- if we could turn to
09:43:04 12 page 99, Mr. Brooks.

09:43:04 13 BY MS. KEANE:

09:43:10 14 Q And the call-out from your slide is on page 99 in a
09:43:15 15 section titled Atherogenic Dyslipidemia, do you see that?

09:43:25 16 A Yes.

09:43:25 17 Q Okay. And why don't we take -- if we could take a look
09:43:27 18 at the ATP III to see if the ATP III actually has a discussion
09:43:31 19 about the causes -- or a discussion about severe
09:43:34 20 hypertriglyceridemia.

09:43:35 21 MS. KEANE: So we're going to turn to page 177.

09:43:43 22 And you see on the left-hand side on page 177,
09:43:50 23 there is a heading there -- actually, Mr. Brooks, if we could
09:43:55 24 go back to the heading of Causes of Elevated Triglyceride.

09:43:55 25 BY MS. KEANE:

09:44:03 1 Q Starting on page 177 there is a discussion of the causes
09:44:05 2 of elevated triglycerides, do you see that?

09:44:11 3 A Yes.

09:44:13 4 Q Okay. And then if you turn, if we take a look at
09:44:15 5 page 178, and within that section there is a discussion with
09:44:22 6 respect to the causes of very high triglycerides. Do you see
09:44:25 7 that?

09:44:25 8 A Yes.

09:44:29 9 Q Okay. And so in the ATP III, when discussing the causes
09:44:37 10 of severe hypertriglyceridemia, the statement in ATP III is
09:44:42 11 that,

09:44:43 12 "When serum triglycerides exceed
09:44:45 13 500 milligrams per deciliter, chylomicrons usually
09:44:50 14 begin to appear in fasting plasma."

09:44:52 15 Do you see that?

09:44:52 16 A Yes.

09:44:53 17 Q And the ATP III, a couple sentences later, goes on to
09:44:57 18 state,

09:44:57 19 "Most frequently reported are genetic defects
09:45:01 20 in lipoprotein lipase or apo C-2."

09:45:10 21 Do you see that?

09:45:11 22 A I do.

09:45:15 23 MS. KEANE: If we could turn to DDX 4.16.

09:45:15 24

09:45:15 25 BY MS. KEANE:

09:45:30 1 Q Dr. Sheinberg, on direct examination you also talked
09:45:32 2 about the Karalis article; is that right?

09:45:36 3 A Yes.

09:45:36 4 Q And, again, on slide 4-16, the slide focuses on one of
09:45:42 5 the quotes from Karalis that you discussed?

09:45:44 6 A Correct.

09:45:44 7 Q Okay. And, again, this is a snippet from a much longer
09:45:49 8 passage in Karalis.

09:45:54 9 A Yes.

09:45:57 10 MS. KEANE: And, Mr. Brooks, if we could pull up
09:46:01 11 Karalis, it's PX 288. If we could go to page 10 of the
09:46:11 12 exhibit. If we go to the column starting with "Patients,"
09:46:17 13 it's the right-hand column.

09:46:17 14 BY MS. KEANE:

09:46:21 15 Q Okay. And you see that the quote from your slide is in
09:46:24 16 the middle of this passage, do you see that?

09:46:27 17 A If you give my just a moment.

09:46:29 18 Q Sure.

09:46:29 19 A (Witness reviews document.)

09:46:34 20 Yes, I do.

09:46:35 21 Q Okay. And if we take a look at the full passage, the
09:46:50 22 paragraph in that right-hand column that starts with,

09:46:53 23 "Patients with very high TG levels may be at
09:46:56 24 an increased CV risk even though their TG levels are
09:47:00 25 lowered to a level at which they are no longer at

09:47:03 1 risk for pancreatitis."

09:47:04 2 Do you see that?

09:47:05 3 A Yes, I do.

09:47:06 4 Q And it goes on to say that,

09:47:08 5 "If an individual with very high TGs falls
09:47:11 6 into one of these patient groups, once the TGs are
09:47:14 7 lowered, consideration should be given to adding a
09:47:17 8 statin to their TG lowering therapy." Correct?

09:47:20 9 A Yes.

09:47:20 10 Q And Karalis is recognizing in this section that some
09:47:30 11 patients will need an addition of a statin on top of their TG
09:47:35 12 lowering therapy.

09:47:36 13 A That's correct. We know that when triglycerides are
09:47:39 14 exceedingly high, the number one risk is pancreatitis because
09:47:42 15 of the way the triglycerides are carried.

09:47:44 16 As the triglycerides are reduced, the carrying
09:47:48 17 molecule really transitions from chylomicrons to VLDL, so the
09:47:53 18 risk of pancreatitis drops, but the cardiovascular risk
09:47:59 19 remains present if not increases.

09:47:59 20 Q And further down if we go to the section that you
09:48:02 21 highlighted, it says that,

09:48:03 22 "If the TG levels fall to a normal or
09:48:05 23 borderline level with lifestyle changes in
09:48:05 24 combination with lipid-lowering therapy,
09:48:11 25 consideration may be given to discontinuing the

09:48:13 1 nonstatin, TG-lowering medication."

09:48:15 2 Do you see that?

09:48:18 3 A Yes, I do.

09:48:19 4 Q And when -- well, I think you discussed in your testimony
09:48:23 5 earlier that triglyceride levels are categorized by various
09:48:27 6 different ranges.

09:48:28 7 A Correct.

09:48:28 8 Q For example, severe hypertriglyceridemia is
09:48:31 9 500 milligrams per deciliter or above?

09:48:33 10 A Well, the definition that we've been using throughout
09:48:36 11 this trial is that it has recently been updated, but, yes,
09:48:40 12 that's the definition we have been using.

09:48:42 13 Q And likewise there's a recognition in the literature that
09:48:46 14 normal triglycerides are triglyceride levels of 150 milligrams
09:48:51 15 per deciliter?

09:48:52 16 A Or less.

09:48:52 17 Q Or less.

09:48:53 18 A Yes.

09:48:53 19 Q Okay. And the literature recognizes that borderline
09:48:56 20 triglycerides are typically 150 milligrams per deciliter to
09:49:00 21 199 milligrams per deciliter.

09:49:02 22 A Yes.

09:49:02 23 Q So in this passage in Karalis, when it discusses the
09:49:07 24 option to consider stopping TG-lowering medication, that is
09:49:11 25 only for patients who have a baseline -- whose baseline level

1 in triglycerides has decreased from over 500 to 200 or 150.

2 A Not necessarily. The reference that I interpret here is
3 that once the risk of pancreatitis is resolved, the acute risk
4 of pancreatitis is resolved, triglyceride levels can continue
5 to be lowered through lifestyle modification, and therefore
6 that triglyceride-lowering medication can be stopped.

7 Again, it's differentiation -- it's differentiating
8 itself from the nonstatin group, not from the statin
9 medicines, because the statin medications continue to cause
10 continued cardiovascular risk reduction.

11 So my reading of this is simply telling me that if
12 lifestyle modifications are continued, the risk of
13 cardiovascular complications can be minimized with the
14 continuation of statins, but the triglyceride-lowering
15 medications can potentially safely be stopped.

16 Q So the Karalis article, you would agree, is a reference
17 that is consistent with how physicians generally practice?

18 A Yes.

19 Q It's a reference that you relied on in both your report
20 and your testimony.

21 A Yes.

22 Q So let's take a look at that -- the statement that you
23 highlighted in your slides.

24 It says,

25 "Consideration may be given to discontinuing

09:50:44 1 the nonstatin TG-lowering medication only after
09:50:47 2 triglyceride levels have fallen to normal or
09:50:51 3 borderline normal levels," correct?

09:50:53 4 A Correct.

09:50:55 5 MS. KEANE: And then if we could scroll down,
09:50:58 6 Mr. Brooks.

09:50:58 7 BY MS. KEANE:

09:50:58 8 Q The passage goes on to say, "The triglyceride levels will
09:51:03 9 need to be monitored clearly for any rise in TG levels."

09:51:06 10 A Correct?

09:51:07 11 Q And that's consistent with your practice as well?

09:51:10 12 A Correct.

09:51:21 13 MS. KEANE: And let's turn to -- I think it's
09:51:27 14 Plaintiffs' Exhibit 289, the medical review.

09:51:27 15 BY MS. KEANE:

09:51:35 16 Q And, again, Dr. Sheinberg, we've discussed the medical
09:51:38 17 review a few times today. This is a document that you've
09:51:42 18 relied on for purposes of your testimony?

09:51:44 19 A Yes.

09:51:44 20 Q And it reflects important background information that
09:51:51 21 physicians would bring to bear in analyzing defendants'
09:51:55 22 labels -- I'm sorry, in reviewing defendants' labels.

09:51:58 23 A Physicians being standard positions in the field?

09:52:03 24 Q Do you agree that -- is it your position that the medical
09:52:07 25 review -- well, let me back up.

09:52:10 1 So your testimony is that the medical review
09:52:16 2 contains important background information that a person of
09:52:19 3 ordinary skill would understand and bring to bear when using
09:52:22 4 defendants' ANDA products as indicated. We've talked about,
09:52:26 5 correct?

09:52:27 6 A Correct.

09:52:27 7 MS. KEANE: Okay. So if we go to page 11, if we
09:52:40 8 take a look at the paragraph at the top of the page.

09:52:40 9 BY MS. KEANE:

09:52:45 10 Q And the medical review states that very high TG, greater
09:52:51 11 than or equal to 500 milligrams per deciliter, has a strong
09:52:55 12 genetic component. Do you see that?

09:52:57 13 A Yes, I do.

09:52:58 14 Q And that's a statement from FDA.

09:53:04 15 A Correct.

09:53:05 16 Q And then it goes on to -- that passage goes on to state
09:53:10 17 that,

09:53:10 18 "The most frequently reported genetic defects
09:53:13 19 for persons with very high triglycerides are in the
09:53:17 20 enzyme lipoprotein lipase, LPL, or in apo C-2, a
09:53:23 21 protein that activates LPL."

09:53:26 22 A Yes, I see that.

09:53:27 23 Q And, again, that's a statement by the FDA.

09:53:30 24 A Yes, it is.

09:53:32 25 Q And that passage goes on to then state that,

09:53:34 1 "The genetic defects result in an inability
09:53:37 2 to break down fatty acids, impaired catabolism of
09:53:45 3 triglyceride-rich lipoproteins" --

09:53:45 4 THE COURT REPORTER: Slow down.

09:53:45 5 MS. KEANE: I apologize. "Impaired" -- let me
09:53:49 6 just -- I'll start from the beginning.

09:53:49 7 BY MS. KEANE:

09:53:51 8 Q The passage goes on to state,

09:53:54 9 "These genetic defects result in the
09:53:56 10 inability to break down fatty acids, impair
09:54:00 11 catabolism of triglyceride-rich lipoproteins. TGRLP
09:54:09 12 also is induced by overproduction of Apop C3, an
09:54:14 13 inhibitor of LPL activity."

09:54:16 14 Do you see that?

09:54:17 15 A Yes, I do.

09:54:18 16 Q Again, this is a statement by FDA.

09:54:20 17 A Yes, it is.

09:54:21 18 MS. KEANE: And if we could turn to the efficacy
09:54:25 19 summary on page 41.

09:54:25 20 BY MS. KEANE:

09:54:36 21 Q And again in this passage FDA states,

09:54:39 22 "Patients with very high TG have a strong
09:54:44 23 genetic component to their disease and have an
09:54:47 24 increased risk for acute pancreatitis."

09:54:49 25 Do you see that?

09:54:49 1 A Yes, I see that.

09:54:50 2 Q And FDA goes on to state at the end of that passage,
09:54:54 3 "Often it is not possible to normalize TGs in
09:54:57 4 these patients."

09:54:58 5 Do you see that?

09:54:59 6 A That's what it says.

09:55:00 7 Q And, again, as we discussed, normal levels are
09:55:04 8 150 milligrams per deciliter or below.

09:55:07 9 A Yes.

09:55:22 10 MS. KEANE: If we could turn to page -- I
09:55:25 11 believe it's page 50 of the same exhibit -- 51.

09:55:25 12 BY MS. KEANE:

09:55:42 13 Q Dr. Sheinberg, do you recall during your testimony
09:55:44 14 earlier today you testified about the chart that is shown on
09:55:51 15 page 50?

09:55:51 16 A Yes.

09:55:52 17 Q And so in the placebo group it notes there 21 percent of
09:55:59 18 patients. Do you see that?

09:56:00 19 A I do.

09:56:01 20 Q So that means in the MARINE trial 80 percent of patients
09:56:04 21 in the placebo group could not get their triglyceride levels
09:56:08 22 below 500 milligrams per deciliter with diet and lifestyle
09:56:13 23 alone.

09:56:15 24 A That -- I think the percentages that you're quoting may
09:56:24 25 be not -- are not accurate. It says that in the placebo

09:56:29 1 group, 79 percent of the people in the placebo group could not
09:56:32 2 reduce their triglycerides with diet and exercise alone.

09:56:36 3 Q Okay. So based on the MARINE study, you would agree that
09:56:44 4 most patients were not able to reduce their triglycerides in
09:56:48 5 the -- let me rephrase.

09:56:50 6 Most patients were not able to reduce their
09:56:53 7 triglycerides with diet and exercise in the placebo group.

09:56:56 8 A Most patients were not, but some patients were.

09:57:00 9 Q So one of the things that you have -- one of the things
09:57:18 10 you discussed earlier, I believe yesterday and this morning,
09:57:22 11 is that, in your opinion, you believe it would be reasonable
09:57:25 12 to stop administration of icosapent ethyl after short-term
09:57:29 13 duration, is that right?

09:57:31 14 A On certain patient populations, yes.

09:57:34 15 Q When patients are on icosapent ethyl therapy, you have no
09:57:42 16 way of knowing when you take a patient off that therapy
09:57:46 17 whether or not their triglyceride levels will increase again
09:57:49 18 or not.

09:57:50 19 A Well, I would argue I do have a way of knowing, and that
09:57:53 20 is from having the patient return for an additional blood draw
09:57:58 21 at some time in the near future.

09:58:02 22 Q And when you say an addition blood draw, do you mean
09:58:04 23 after they have ceased icosapent ethyl therapy?

09:58:06 24 A Correct.

09:58:06 25 Q But at the time that you -- that you would advise the

09:58:09 1 patient to stop taking icosapent ethyl therapy you have no way
09:58:13 2 of knowing at that point in time whether or not their
09:58:16 3 triglyceride levels will increase after that therapy is
09:58:19 4 discontinued.

09:58:20 5 A I would disagree with that statement.

09:58:22 6 I have a good understanding of what would likely
09:58:27 7 happen based on the patient's improvement in lifestyle,
09:58:32 8 improvements in body mass, and their improvements in
09:58:36 9 potentially finger-stick glucose measurements.

09:58:40 10 So there's a bunch of clinical data that I could
09:58:43 11 rely on that would suggest to me that this individual may have
09:58:47 12 success if we stop the medication.

09:58:48 13 Q And, again, it's "may have success." You don't know for
09:58:52 14 sure whether or not those patient's triglyceride levels will
09:58:54 15 go back up again.

09:58:55 16 A That's the beauty of medicine. We don't know for sure
09:58:58 17 anything, so I would not know for sure.

09:59:06 18 MS. KEANE: And, Mr. Brooks, if we could take a
09:59:09 19 look in the same document at page 48.

09:59:09 20 BY MS. KEANE:

09:59:20 21 Q And here, Dr. Sheinberg, do you see on page 48 there's a
09:59:23 22 section entitled 6.1.4, Analysis of Primary Endpoints, do you
09:59:29 23 see that?

09:59:29 24 A Yes, I do.

09:59:30 25 Q Okay. So I want to continue down in that section, and if

09:59:35 1 it's helpful for you, Dr. Sheinberg, I believe there's a copy
09:59:38 2 of this in your binder, but I then want to turn to page 55 in
09:59:41 3 this section.

09:59:47 4 MS. KEANE: If we take a look at page 55,
09:59:50 5 Mr. Brooks, at the top of the page, could you pull up the
09:59:52 6 reviewer comment?

09:59:52 7 BY MS. KEANE:

09:59:56 8 Q And, Dr. Sheinberg, you understand that this is still
09:59:59 9 part of the discussion of the primary efficacy endpoint in the
10:00:02 10 medical review?

10:00:03 11 A Yes.

10:00:04 12 Q And the FDA states there that,

10:00:09 13 "Although the Vascepa 2-gram dose reduced TG,
10:00:13 14 the potency of the dose was such that there were wide
10:00:16 15 fluctuations in TG levels."

10:00:18 16 A I see that.

10:00:19 17 Q And then FDA goes on to state that,

10:00:23 18 "The slight improvements to TG levels
10:00:25 19 achieved with the Vascepa 2-gram dose at week 4 were
10:00:29 20 reduced back to almost the baseline TG."

10:00:33 21 Do you see that?

10:00:33 22 A I do.

10:00:34 23 Q And in contrast to that, FDA states that,

10:00:37 24 "The 4-gram dose showed none of the wide
10:00:40 25 fluctuations seen in 2 grams or placebo."

10:00:44 1 Do you see that?

10:00:45 2 A Yes, I do.

10:00:46 3 Q And so FDA -- in FDA's review of the data from the MARINE
10:00:52 4 trial, FDA's conclusion was that not even 2 grams of Vascepa
10:00:56 5 could reduce and maintain triglyceride levels in patients with
10:01:00 6 severe hypertriglyceridemia.

10:01:01 7 A Correct.

10:01:02 8 Q And, certainly, if the 2 grams of Vascepa -- 2 grams per
10:01:09 9 day of Vascepa could not reduce and maintain the triglyceride
10:01:13 10 levels, the placebo group was also not -- the TG levels in the
10:01:17 11 placebo group were also not reduced and maintained.

10:01:21 12 A Well, we showed that 21 percent of that group did have a
10:01:25 13 reduction in the maintenance of triglyceride levels.

10:01:28 14 Q And one of the things that FDA points to in its analysis
10:01:40 15 is that there were wide fluctuations in TG that were observed
10:01:44 16 in the placebo group, correct?

10:01:46 17 A That's correct.

10:01:47 18 Q And, in fact, FDA distinguishes the Vascepa 4 grams per
10:01:51 19 dose from the placebo group there in the last statement and
10:01:55 20 says, "the ability to eliminate the wide fluctuations seen in
10:01:59 21 the placebo group."

10:02:01 22 Do you see that?

10:02:01 23 A If I may read the sentence in its entirety.

10:02:05 24 Are we talking about the last sentence in the second
10:02:09 25 paragraph?

10:02:10 1 Q Yes.

10:02:25 2 A Yes, I see that.

10:02:53 3 MS. KEANE: Dr. Sheinberg -- or, Mr. Brooks, if
10:02:56 4 we could turn to DDX 4.15.

10:02:56 5 BY MS. KEANE:

10:03:04 6 Q And, Dr. Sheinberg, DDX 4.15 is a slide that you used in
10:03:09 7 your direct testimony?

10:03:09 8 A Yes, it is.

10:03:10 9 Q And, again, here you relied on a passage from DX 1960?

10:03:18 10 A That is correct.

10:03:19 11 Q And this is a -- this is a Miller chapter in a book from
10:03:25 12 2009?

10:03:25 13 A Yes, it is.

10:03:28 14 MS. KEANE: So let's if we could turn to --
10:03:30 15 actually turn to DX 1960, and, Mr. Brooks, if we could go to
10:03:38 16 the passage on page 38.

10:03:38 17 BY MS. KEANE:

10:03:44 18 Q Okay. And do you recall, Dr. Sheinberg, that the passage
10:03:47 19 on page 38, sections of this are what you cited in your
10:03:52 20 slides?

10:03:52 21 A Yes, ma'am.

10:03:53 22 Q And that the statement that you highlighted in your
10:03:56 23 discussion today is that final statement,

10:04:00 24 "Regardless of the macronutrient intake, the
10:04:03 25 most potent manner for reducing TG is through weight

10:04:07 1 reduction."

10:04:08 2 A That's what -- I'm sorry, your question was is that what
10:04:11 3 is says there or -- what was the question?

10:04:12 4 Q I'm sorry. My question is -- and we can go back, maybe
10:04:16 5 we can put up DDX 4.15 beside it.

10:04:19 6 My question for you is simply that the statement
10:04:23 7 that you highlighted in your direct testimony is that
10:04:26 8 statement at the end of DDX 4.15, which states,

10:04:29 9 "Regardless of the macronutrient intake, the
10:04:32 10 most potent manner for reducing TG is through weight
10:04:35 11 reduction."

10:04:36 12 Do you see that?

10:04:37 13 A That is correct.

10:04:39 14 MS. KEANE: And, now, if we could turn back to
10:04:43 15 DX 1960. Mr. Brooks, if you could pull out a little bit so we
10:04:50 16 could see the full section.

10:04:50 17 BY MS. KEANE:

10:04:54 18 Q So the title of this section with the statement that you
10:04:59 19 quoted is Efficacy of Dietary Treatment and Weight Reduction.
10:05:03 20 Do you see that?

10:05:03 21 A Yes, I do.

10:05:06 22 Q The statement that you refer to in your slides that
10:05:10 23 states -- that refers to the most potent manner for reducing
10:05:13 24 TG is through weight reduction, that's a reference to the most
10:05:16 25 potent manner of dietary treatment -- of dietary or lifestyle

10:05:23 1 modifications, correct?

10:05:24 2 A Yes, it is.

10:05:28 3 Q In fact, if we go down to the discussion about dietary
10:05:38 4 and weight reduction, after the statement that you highlighted
10:05:42 5 in your direct testimony, there is additional information
10:05:45 6 provided there.

10:05:46 7 Do you see that?

10:05:46 8 A Yes.

10:05:47 9 Q Okay. In the last sentence there it highlights a
10:05:51 10 meta-analysis of 70 diet studies, and those studies found that
10:05:57 11 each 2.2 pounds of weight loss was associated with a
10:06:01 12 1.3 milligram per deciliter reduction in triglycerides.

10:06:06 13 Do you see that?

10:06:07 14 A Yes.

10:06:07 15 Q And you didn't include that sentence in your
10:06:09 16 demonstratives.

10:06:10 17 A I did not.

10:06:11 18 Q One of the examples you discussed during your direct
10:06:17 19 testimony today -- or I believe it was yesterday, was an
10:06:20 20 example where a patient reduces triglyceride levels from
10:06:24 21 500 milligrams per deciliter to 300 milligrams per deciliter.

10:06:28 22 Do you recall that?

10:06:29 23 A I do.

10:06:29 24 Q And you would agree with me that in order for a patient
10:06:41 25 to reduce their triglyceride levels from 500 milligrams --

10:06:46 1 from 550 milligrams per deciliter to 300 milligrams per
10:06:52 2 deciliter, based on the passage that you have cited, that
10:06:55 3 would be a significant weight reduction.

10:06:57 4 A Yes, but not necessarily, because you're forgetting to
10:07:00 5 include increases in exercise component.

10:07:05 6 Q Okay. So there would be some corresponding additional
10:07:10 7 perhaps triglyceride reduction from exercise?

10:07:13 8 A Yes, that is correct.

10:07:14 9 MS. KEANE: Okay. So if we could -- Mr. Brooks,
10:07:24 10 if we could pull up PDX 3-6.

10:07:24 11 BY MS. KEANE:

10:07:36 12 Q And, Mr. Brooks -- I'm sorry, Dr. Sheinberg, do you see
10:07:39 13 there we have listed your example of 550 milligrams per
10:07:43 14 deciliter at the first visit, and 300 milligrams per deciliter
10:07:47 15 at the second visit? Do you see that?

10:07:49 16 A Correct.

10:07:49 17 Q And that would be a reduction of 250 milligrams per
10:07:54 18 deciliter.

10:07:54 19 A Correct.

10:07:54 20 Q Okay. And so if we take the information from the Miller
10:07:58 21 reference, and use the ratio that's disclosed there --

10:08:02 22 MS. KEANE: Mr. Brooks, if you could pull up the
10:08:04 23 math.

10:08:04 24
10:08:04 25 BY MS. KEANE:

10:08:07 1 Q Would you generally agree with me that that's how we
10:08:10 2 would do the math to figure out how much of a weight loss you
10:08:13 3 would need to see a 250-milligram per deciliter reduction?

10:08:17 4 A That is assuming that that is the only thing that
10:08:20 5 individual is doing.

10:08:21 6 We know that there can be -- so when we talk about
10:08:23 7 weight loss, weight loss is really not a good indicator of
10:08:28 8 body mass or body fat. So there can be essentially no weight
10:08:32 9 loss with a conversion of fat to muscle.

10:08:36 10 So weight loss is one potential mechanism. But if
10:08:39 11 you convert abdominal adiposity or abdominal fat to skeletal
10:08:45 12 muscle, this doesn't take into consideration that.

10:08:47 13 So I agree that weight loss at 2 point -- according
10:08:50 14 to this article a weight lost of 2.2 pounds is associated with
10:08:55 15 a 1.3 milligram per deciliter reduction, but this has no
10:09:00 16 bearing on the entire picture because nothing else is
10:09:04 17 constant.

10:09:04 18 If we remove sugars, because we know our body
10:09:08 19 handles a hundred calories of sugar --

10:09:11 20 Q So, Dr. Sheinberg, if you could just focus on the
10:09:15 21 question.

10:09:15 22 A Okay.

10:09:16 23 Q So let's go back then to your slide, the slide that you
10:09:19 24 prepared for your testimony today with counsel, DDX 4.15.

10:09:28 25 The statement that you included in this slide is

10:09:30 1 that, "Regardless of macronutrient intake" -- I'm sorry, let
10:09:35 2 me rephrase it.

10:09:36 3 "Regardless of macronutrient intake, the most
10:09:40 4 potent manner for reducing TG is through weight
10:09:43 5 reduction."

10:09:43 6 Do you see that?

10:09:44 7 A Yes.

10:09:45 8 Q And that is the statement that you included during your
10:09:47 9 direct testimony.

10:09:48 10 A It is.

10:09:48 11 Q So we go back to where we were with PDX 3-6. Okay? So
10:09:55 12 we do that calculation, the resulting weight loss is
10:09:59 13 423 pounds.

10:10:00 14 Do you see that?

10:10:00 15 A I see that's what's on the screen.

10:10:02 16 Q And you would agree with me that that's not a reasonable
10:10:05 17 weight loss to expect with any patient.

10:10:08 18 A Of course not in a time frame that I have given. But,
10:10:12 19 again, my slide takes into consideration not just weight loss.

10:10:17 20 MS. KEANE: Okay. If we could take a look at --
10:10:40 21 if we could go to PDX -- I'm sorry, that's not correct. If we
10:10:51 22 could go to PDX 4-3.

10:10:51 23 BY MS. KEANE:

10:11:00 24 Q And, Dr. Sheinberg, these are summaries of your opinions
10:11:03 25 from earlier during your testimony today?

10:11:06 1 A Yes, ma'am, it is.

10:11:08 2 Q And one of the statements included here, the second --
10:11:18 3 I'm sorry, the first bullet point says,

10:11:21 4 "Severe hypertriglyceridemia is not
10:11:22 5 necessarily a chronic condition requiring indefinite
10:11:25 6 drug treatment."

10:11:26 7 Do you see that?

10:11:27 8 A Yes, I do.

10:11:27 9 Q And so if we took that statement and edited it to say,
10:11:32 10 "Severe hypertriglyceridemia is never a
10:11:36 11 chronic condition requiring indefinite drug
10:11:39 12 treatment," that statement would be incorrect.

10:11:43 13 A I don't like to use never or always. I think those are
10:11:47 14 overly generalized terms which never really apply -- or don't
10:11:52 15 apply.

10:11:53 16 Q And so you agree with me that sometimes severe
10:11:57 17 hypertriglyceridemia is a chronic condition that requires
10:11:59 18 indefinite drug treatment.

10:12:00 19 A Yes, I do.

10:12:01 20 Q And, in fact, there are some patients with severe
10:12:06 21 hypertriglyceridemia whose triglyceride levels will never get
10:12:10 22 under 500.

10:12:11 23 A That is correct.

10:12:13 24 Q And that's despite what medications the patient takes.

10:12:17 25 A That is correct.

10:12:17 1 Q And if the patient -- if a patient is not able to get
10:12:21 2 their triglyceride levels below 500, they have an underlying
10:12:25 3 chronic problem.

10:12:27 4 A That is correct.

10:12:28 5 Q And at least for those patients, icosapent ethyl is
10:12:32 6 prescribed long-term.

10:12:34 7 A Yes, that is correct.

10:12:35 8 Q And that prescription is within the indication of
10:12:42 9 defendants' labeling.

10:12:43 10 A Yes.

10:12:43 11 Q And, in fact, the labeling would encourage long-term
10:12:48 12 administration in those patients.

10:12:55 13 A The label -- and if you could pull up the label, I could
10:12:59 14 cite it more particularly, but the label is really silent on
10:13:03 15 the duration of therapy. It simply indicates the target
10:13:07 16 population for which this drug is indicated and for which it
10:13:12 17 should be used.

10:13:14 18 MS. KEANE: Mr. Brooks, if we could go to
10:13:22 19 PDX 3-5.

10:13:22 20 BY MS. KEANE:

10:13:31 21 Q And, again, Dr. Sheinberg, the information shown on
10:13:37 22 PDX 3-5 is testimony from Mr. Mathers. Do you see that?

10:13:41 23 A Yes.

10:13:41 24 Q And we've discussed Mr. Mathers a few times today.

10:13:45 25 A Yes.

1 Q And Mr. Mathers, during his deposition, was asked the
2 question,

3 "Now, a drug can be approved for long-term
4 use without using the term chronic or the term
5 long-term in the indications and usage or dosage and
6 administration sections, correct?"

7 Do you see that?

8 A Yes, I do.

9 Q And then he responded,

10 "I don't think those characterizations are
11 necessary in order for the drug to be approved for
12 use for an indefinite time period as long as it's
13 within -- as long as it's within the scope of the
14 intended patient population and the physician
15 believes that they would continue to benefit from the
16 drug or are continuing to benefit from it."

17 Do you see that?

18 A I do.

19 Q And do you disagree with Mr. Matters?

20 A No, I agree with Mr. Mathers that basically says it's
21 left up to the discretion of the physician.

22 Q And Mr. Mathers purports to be an expert in FDA
23 regulatory issues?

24 A Correct.

25 Q And you are not an expert in regulatory issues?

10:14:53 1 A I am not.

10:14:54 2 Q And you're not an expert in drug approval?

10:14:57 3 A No, I am not.

10:14:58 4 Q And you're not an expert in FDA labeling discussions?

10:15:02 5 A I am not.

10:15:12 6 MS. KEANE: And, Mr. Brooks, could we go to
10:15:17 7 PDX 3-4.

10:15:17 8 BY MS. KEANE:

10:15:21 9 Q And, Dr. Sheinberg, shown on PDX 3-4 we have testimony
10:15:27 10 from Dr. Edward Fisher. Do you see that?

10:15:30 11 A Yes, I do.

10:15:31 12 Q Do you know Dr. Fisher?

10:15:33 13 A I've had the opportunity to meet him during this trial.

10:15:35 14 Q And you understand that Dr. Fisher is one of defendants'
10:15:39 15 experts in this case?

10:15:40 16 A Yes, I do.

10:15:42 17 Q And you'll see on PDX 3-4, during his deposition
10:15:48 18 Dr. Fisher was asked,

10:15:49 19 "Vascepa's indication informs doctors that it
10:15:52 20 may sometimes be necessary to keep severely
10:15:55 21 hypertriglyceridemic patients on Vascepa in order to
10:15:59 22 reduce triglycerides below 500 milligrams per
10:16:03 23 deciliter, and maintain them below that level,
10:16:07 24 correct?"

10:16:07 25 And then his response was yes.

10:16:09 1 Do you see that?

10:16:10 2 A Yes, I do.

10:16:11 3 Q Do you agree with Dr. Fisher?

10:16:13 4 A Yes, it may sometimes be necessary.

10:16:24 5 Q So we spent a little bit of time talking about patients
10:16:28 6 who would not be able to get below 500 milligrams per
10:16:31 7 deciliter.

10:16:31 8 There are also patients with severe
10:16:33 9 hypertriglyceridemia whose triglyceride levels will not ever
10:16:36 10 get below 500 milligrams per deciliter without medication; is
10:16:41 11 that correct?

10:16:42 12 A That is correct.

10:16:42 13 Q And for those patients as well, Vascepa -- or icosapent
10:16:46 14 ethyl would be prescribed for long-term use.

10:16:48 15 A Yes, that is correct.

10:16:50 16 Q And you would agree with me that there are patients with
10:16:53 17 severe hypertriglyceridemia who manage to get their
10:16:56 18 triglycerides under 500 but can't maintain that level without
10:17:00 19 medication.

10:17:02 20 A Yes, there are patients that can do that.

10:17:05 21 Q And for those patients -- and for those patients,
10:17:15 22 icosapent ethyl would also be prescribed long-term.

10:17:19 23 A Yes, that is correct.

10:17:20 24 Q And those -- and with respect to those patients, that
10:17:28 25 long-term use would fall within the indication in defendants'

10:17:31 1 labeling.

10:17:32 2 A Again, the defendants' labeling does not mention any
10:17:36 3 duration or specific time frame or specific patient population
10:17:44 4 outside of the individual having -- being an adult and having
10:17:48 5 triglycerides over 500.

10:17:51 6 Q And so -- and then, in your view, my understanding is
10:17:54 7 that there are additional patients who may reduce their
10:17:58 8 triglyceride levels with icosapent ethyl and then be able to
10:18:02 9 maintain their reduced triglyceride levels with diet and
10:18:06 10 exercise.

10:18:07 11 A That is correct.

10:18:07 12 Q And you would agree with me that those patients who are
10:18:12 13 able to reduce their triglycerides below 500 and maintain that
10:18:17 14 reduction, that those patients do not fall within the scope of
10:18:21 15 the label.

10:18:23 16 A I would not agree with that statement.

10:18:26 17 MS. KEANE: Okay. And if we could go to
10:18:39 18 Dr. Sheinberg's report, DX 1697, go to paragraph 68.

10:18:39 19 BY MS. KEANE:

10:18:54 20 Q Dr. Sheinberg, your expert report is sworn testimony,
10:18:57 21 correct?

10:18:57 22 A Correct.

10:18:58 23 Q In paragraph 68 of your expert report, the first sentence
10:19:05 24 states that,

10:19:06 25 "Vascepa and defendants' ANDA products are

10:19:09 1 also not indicated to reduce triglycerides in
10:19:12 2 patients who do not require drug therapy to maintain
10:19:15 3 triglyceride levels below 500 milligrams per
10:19:19 4 deciliter."

10:19:20 5 Do you see that?

10:19:20 6 A Correct.

10:19:21 7 Q Is that statement correct?

10:19:22 8 A Yes.

10:19:23 9 Q And that's an accurate representation of your testimony.

10:19:38 10 A That is correct.

10:20:03 11 MS. KEANE: Your Honor, I don't have any further
10:20:05 12 questions at this time.

10:20:05 13 REDIRECT EXAMINATION

10:20:05 14 BY MR. REIG-PLESSIS:

10:20:36 15 Q Dr. Sheinberg, do you recall Ms. Keane asking you about
10:20:39 16 statements in your expert report in which you relied on
10:20:42 17 Mr. Mathers' report?

10:20:43 18 A Yes, I do.

10:20:44 19 MR. REIG-PLESSIS: So could we pull up DX 1697,
10:20:50 20 and could we go to paragraph 64.

10:20:50 21 BY MR. REIG-PLESSIS:

10:21:11 22 Q Was it your understanding from the expert report of
10:21:14 23 Mr. Mathers that,

10:21:15 24 "FDA regulations regarding the indications
10:21:18 25 and usage section of a drug label state that a drug's

10:21:22 1 indications or uses must not be implied or suggested
10:21:26 2 in other sections of the labeling if not included in
10:21:29 3 this section"?

10:21:31 4 And there's a cite to the federal regulations.

10:21:33 5 A Yes, I do.

10:21:36 6 MR. REIG-PLESSIS: And could we now go to
10:21:38 7 paragraph 80 of DX 1697.

10:21:38 8 BY MR. REIG-PLESSIS:

10:21:55 9 Q And was it your understanding from Mr. Mathers' report
10:21:58 10 that FDA guidance states that,

10:22:00 11 "The clinical studies section must not
10:22:04 12 suggest or imply indications, uses, or dosing
10:22:08 13 regimens not stated in the indications and usage or
10:22:12 14 dosage and administration section"?

10:22:14 15 And that's a quote from the FDA's clinical
10:22:17 16 studies guidance.

10:22:18 17 A I do, and that is why, when questioned about the time
10:22:22 18 frame in the MARINE study under the study section, I don't
10:22:27 19 look at that time frame as a direct instruction or reflection
10:22:31 20 of how to use this medication.

10:22:33 21 Q Now, do you recall Ms. Keane asking whether it's possible
10:22:39 22 that some physicians following the label might infringe?

10:22:42 23 A Yes, I do.

10:22:43 24 Q Just to be clear, is there any actual instruction
10:22:47 25 directed to any physicians in the label to administer

10:22:50 1 defendants' products for at least 12 weeks?

10:22:53 2 A There are none.

10:22:54 3 Q And do you recall Ms. Keane asking you about the effect
10:22:58 4 that weight loss would have on triglyceride reduction?

10:23:02 5 A Yes, I do.

10:23:03 6 Q Is weight loss the only lifestyle modification that a
10:23:07 7 physician can use to reduce triglycerides?

10:23:09 8 A Absolutely not.

10:23:10 9 Q What are some other lifestyle modifications that could be
10:23:15 10 used to reach that goal?

10:23:16 11 A Discontinuation of sugared beverages, discontinuation of
10:23:22 12 alcohol, discontinuation of tobacco products, and the
10:23:26 13 development and successful engagement into an exercise regimen
10:23:32 14 consisting mostly the aerobic exercise, but also some
10:23:38 15 anaerobic exercise to increase lean muscle mass.

10:23:41 16 Q And could those lifestyle modifications produce
10:23:44 17 significant reductions in triglycerides?

10:23:46 18 A Yes, they absolutely can and do very frequently.

10:23:49 19 Q And can they be used to maintain significant triglyceride
10:23:53 20 reductions?

10:23:53 21 A Yes, they can.

10:23:55 22 Q And do you recall Ms. Keane asking you about the supply
10:23:58 23 of Vascepa that's provided by your prescriptions to patients?

10:24:03 24 A Yes, I do.

10:24:04 25 Q Is the reason that you prescribe three months with three

10:24:07 1 refills in order to reduce or maintain triglycerides below
10:24:08 2 500?

10:24:13 3 A I'm sorry --

10:24:14 4 Q Sure. Is the reason that you prescribe three months with
10:24:18 5 three refills of Vascepa in order to reduce or maintain
10:24:22 6 triglycerides below 500 or is it for other reasons?

10:24:25 7 A It is not, it's for other reasons.

10:24:27 8 Q Do you ever discontinue Vascepa before a patient's
10:24:32 9 three-month prescription is complete?

10:24:35 10 A Yes, I do.

10:24:36 11 Q Can patients stop taking Vascepa even if they still have
10:24:40 12 pills left in their prescription?

10:24:42 13 A They frequently do.

10:24:44 14 Q Now, apart from your standard prescriptions, is there any
10:24:45 15 other way in which you provide Vascepa to patients?

10:24:46 16 A Yes. We can give the patients samples which are provided
10:24:50 17 by the manufacturer.

10:24:51 18 Q And how many pills are in a sample?

10:24:54 19 A Currently the samples or the samples I have used contain
10:24:59 20 a small pill bottle with two days worth of samples, so eight
10:25:04 21 pills per bottle.

10:25:05 22 And when I prescribe this type of medication, I will
10:25:08 23 typically give an individual eight to 15 bottles if I have
10:25:16 24 them available.

10:25:17 25 Q So if you give a patient samples of Vascepa, would that

1 be a 12-week supply?

2 A It would not.

3 MR. REIG-PLESSIS: So, Mr. Gross, staying on
4 DX 1697, Dr. Sheinberg's report, could we go back up to
5 paragraph 68 which is -- I apologize, I don't have the page
6 number of the exhibit. But -- there it is.

7 BY MR. REIG-PLESSIS:

8 Q And, Dr. Sheinberg, by this paragraph what did you mean?

9 A So the paragraph basically states that once a patient's
10 triglycerides fall below 500, and the use of Vascepa is no
11 longer needed to maintain triglyceride levels, the patient's
12 continued treatment with Vascepa or the ANDA product would
13 fall to an off-label use that is not within the approved
14 indication.

15 Q So by that statement were you implying in any way that
16 the indicated use for Vascepa or defendants' ANDA products is
17 limited to treating patients who require chronic therapy for
18 triglyceride reduction?

19 A I am not. The indication in my practice to use this
20 medicine -- or the reason I use this medicine long-term is
21 very minimally to reduce triglycerides or maintain
22 triglycerides less than 500.

23 As I testified earlier, I use this medication for
24 the beneficial impact it has across the board of advanced
25 lipid panel biomarkers.

10:27:08 1 I use this medication routinely to reduce
10:27:12 2 intravascular inflammation which is simply inflammation of the
10:27:16 3 blood vessels which is a precursor of a heart attack, and I've
10:27:21 4 been very successful in using this medication to do so.

10:27:24 5 Q And if a patient's underlying lifestyle cause of high
10:27:28 6 triglycerides is removed, does a patient require Vascepa
10:27:30 7 anymore for the indicated purpose of the MARINE indication?

10:27:33 8 A They do not. The -- like I said, they do not require it
10:27:38 9 for this indicated purpose. That does not mean they still
10:27:41 10 don't have benefit in these other areas which I described, but
10:27:45 11 very rarely is it to maintain triglycerides below 500 in my
10:27:50 12 practice.

10:27:50 13 Q So once the underlying cause of this hypertriglyceridemia
10:27:57 14 caused by lifestyle issues is removed, would the continued use
10:28:00 15 of Vascepa to reduce triglycerides at that point become an
10:28:05 16 off-label use from defendants' ANDA products?

10:28:09 17 A Yes, it would.

10:28:10 18 MR. REIG-PLESSIS: No further questions, thank
10:28:11 19 you.

10:28:17 20 THE COURT: Ms. Keane?

10:28:19 21 MS. KEANE: No, Your Honor. I don't have any
10:28:21 22 further questions.

10:28:22 23 THE COURT: All right. Thank you.

10:28:23 24 Dr. Sheinberg is excused, and I think this is a
10:28:27 25 good time for us to take our morning break.

10:28:27 1 (The witness was excused.)

10:28:27 2 (A recess was taken.)

10:39:34 3 THE COURT: Please be seated.

10:48:11 4 Who is the defendants' next witness?

10:48:17 5 MS. HEYDORN: Your Honor, before we proceed with
10:48:19 6 our next witness, this is Alison Heydorn for defendants.

10:48:22 7 THE COURT: Would you pull -- either speak up or
10:48:25 8 pull the microphone closer to you.

10:48:28 9 MS. HEYDORN: At this time, defendants would
10:48:29 10 like to offer deposition testimony into the record.

10:48:32 11 As plaintiff's explained earlier this week, we
10:48:35 12 plan to give you a list of the designated testimony now, and
10:48:39 13 then the parties will provide joint highlighted copies of the
10:48:43 14 transcripts at the conclusion of trial.

10:48:45 15 Defendants' also move to admit the exhibits that
10:48:50 16 are referenced in the deposition testimony at this time.

10:48:54 17 May I list the exhibit numbers?

10:48:56 18 THE COURT: Yes.

10:48:58 19 MS. HEYDORN: DX 1543 --

10:49:00 20 THE COURT: Give me one moment.

10:49:12 21 All right. Now I'm ready. Thank you.

10:49:17 22 MS. HEYDORN: DX 1543, DX 1730, DX 1731,
10:49:23 23 DX 1732, DX 1733, DX 1734, DX 1735, DX 1736, DX 1737, DX 1738,
10:49:43 24 DX 1739, DX 1740, DX 1741, DX 1742, DX 1743, DX 1745, DX 1747,
10:50:04 25 DX 1750, DX 1793, DX 1797, DX 1853, DX 1854, DX 1855, DX 1856,

10:50:24 1 DX 1857, DX 1858, DX 1859, DX 1860, DX 1861, DX 1862, DX 1881,
10:50:46 2 DX 1882, DX 1883, DX 1884, DX 1885, DX 1886, DX 1887, DX 1888,
10:51:05 3 DX 1889, and DX 1890.

10:51:18 4 THE COURT: Any objection to those exhibits?

10:51:22 5 MS. KEANE: No, Your Honor.

10:51:23 6 THE COURT: All right. Thank you.

10:51:24 7 The exhibits are admitted, and then I will
10:51:26 8 accept the deposition testimony as I did with the plaintiff's
10:51:31 9 proffer. Thank you.

10:51:34 10 MS. HEYDORN: Thank you. May I approach with a
10:51:36 11 flash drive?

10:51:37 12 THE COURT: Yes. Thank you.

10:51:39 13 (Defendants' Exhibits 1543, 1730 through
10:49:20 14 1743, 1745, 1747, 1750, 1793, 1797, 1853
10:50:16 14 through 1862, and 1881 through 1890
10:51:40 received in evidence.)

10:51:44 15 MR. REIG-PLESSIS: Yes, Your Honor. Eimeric
10:51:59 16 Reig for the defendants.

10:52:00 17 In light of the testimony that's already been
10:52:01 18 elicited in today's and yesterday's testimony, defendants'
10:52:06 19 will not be calling their FDA regulatory expert Mr. Mathers,
10:52:11 20 and we will be proceeding with the obviousness portion of our
10:52:15 21 case.

10:52:16 22 THE COURT: All right. Give me one moment to
10:52:18 23 make that note.

10:52:44 24 Thank you. Let's proceed.

10:52:45 25 MR. REIG-PLESSIS: As their next witness,

10:52:46 1 defendants call Dr. Jay Heinecke.

10:52:53 2 THE CLERK: Please come forward.

10:52:53 3 JAY WALTER HEINECKE, M.D.,
10:52:53 4 called as a witness on behalf of the Defendant,
10:52:59 4 was sworn and testified as follows:

10:52:59 5 THE CLERK: Please be seated.

10:53:11 6 Please state for the record your full name and
10:53:15 7 spell your last name.

10:53:17 8 THE WITNESS: My full name is Jay Walter
10:53:22 9 Heinecke. J-a-y. H-e-i-n-e-c-k-e.

10:53:29 10 THE COURT: Please proceed.

10:53:30 11 DIRECT EXAMINATION

10:53:30 12 BY MR. REIG-PLESSIS:

10:53:30 13 Q Good afternoon, Dr. Heinecke.

10:53:33 14 Where are you currently employed?

10:53:36 15 A I'm currently employed as a Professor of Medicine at the
10:53:40 16 University of Washington in Seattle.

10:53:43 17 Q Did defendants retain you to testify as an expert in this
10:53:46 18 case?

10:53:47 19 A Yes, they did.

10:53:48 20 Q And apart from this case, do you have any affiliation
10:53:51 21 with the defendants outside of this case?

10:53:53 22 A No, I don't.

10:53:54 23 Q What is your area of expertise?

10:53:57 24 A Lipoprotein metabolism and the pathogenesis of
10:54:03 25 atherosclerosis, otherwise known as hardening of the arteries.

10:54:06 1 Q So if we could turn to DDX 6.1. There's a snapshot on
10:54:11 2 the screen of DX 2222, page 1, which is in your binder. Could
10:54:17 3 you identify this document, please.

10:54:18 4 A Yes. This is a copy of my Curriculum Vitae that was
10:54:23 5 submitted to counsel when I was retained in the fall of 2018.

10:54:27 6 MR. REIG-PLESSIS: And defendants move the
10:54:28 7 admission of DX 2222.

10:54:30 8 MR. SIPES: No objection, Your Honor.

10:54:31 9 THE COURT: DX 2222 is admitted.

10:54:31 10 (Defendants' Exhibit 2222 received in
10:54:35 11 evidence.)

10:54:35 11 BY MR. REIG-PLESSIS:

10:54:35 12 Q Does your CV accurately list your publications and honors
10:54:40 13 over the course of your career at the time it was created?

10:54:42 14 A I believe there's been about 10 subsequent publications,
10:54:46 15 but otherwise it's accurate.

10:54:47 16 Q So turning to DDX 6.2, there's another snapshot of
10:54:52 17 DX 2222, could you briefly summarize your educational
10:54:58 18 background.

10:54:58 19 A Yes. I went to the Medical School at Washington
10:55:01 20 University School of Medicine in St. Louis. I did my training
10:55:06 21 in internal medicine and a post-doctoral fellowship at the
10:55:10 22 University of Washington.

10:55:12 23 This sometimes confuses people because Washington
10:55:12 24 University is in St. Louis and the University of Washington is
10:55:16 25 in Seattle.

1 I'd like to emphasize that I did a post-doctoral
2 fellowship in the Division of Metabolism, Endocrinology, and
3 Nutrition with a special emphasis on disorders of lipid
4 metabolism. I also worked in the lipid clinic there, as well
5 as subsequently when I was a junior faculty.

6 The lipid clinic at the University of Washington had
7 a special interest in disorders of triglyceride, metabolism,
8 and diabetes.

9 Q Turning to DDX 6.3, have you taught courses relating to
10 lipid disorders?

11 A Yes. I've taught continuing medical education courses to
12 physicians on hyperlipidemia, diabetes, and atherogenesis.
13 And, as I mentioned before, atherogenesis is trying to
14 understand the causes of hardening of the artery.

15 I've also taught the endocrine core course both at
16 the University of Washington and at Washington University,
17 focused on diabetes and disorders of lipoprotein metabolism.

18 I also give lectures on lipoprotein metabolism and
19 atherogenesis to the Fellows in the Department of Medicine at
20 the University of Washington.

21 Q Have you treated patients with lipid disorders?

22 A I have. In addition to my post-doctoral training, where
23 I was in lipid clinic at the University of Washington, which
24 was from 1984 to 1991, I also was a attending and lipid clinic
25 at Washington University of School of Medicine from 1992 to

2002.

And when I returned to the University of Washington as a full professor in 2002, I became an attending in lipid clinic, where I served from 2003 until 2008 or 2009 when I stopped seeing patients.

Q And specifically, have you treated patients with triglycerides above 500?

A Yes, I have.

Q Have you administered Omega-3 fatty acids, such as EPA and DHA, to treat patient with elevated triglycerides?

A Yes, I have.

Q Have you also published on the topic of lipoproteins and atherosclerosis?

A Yes. I have more than 200 publications on lipoproteins and heart disease.

MR. REIG-PLESSIS: Defendants' tender --

THE COURT: Dr. Heinecke, would you move closer to the microphone --

THE WITNESS: Yes. Sorry about that.

THE COURT: -- or raise your voice. Thank you.

THE WITNESS: Just to answer the last question, I have more than 200 publications on lipoproteins and heart disease.

Is that better, Your Honor?

THE COURT: Yes. Thank you.

10:57:58 1 MR. REIG-PLESSIS: Defendants' tender
10:58:00 2 Dr. Heinecke as an expert in the fields of lipoprotein
10:58:03 3 metabolism and lipid disorders.

10:58:06 4 MR. SIPES: No objection, Your Honor.

10:58:06 5 THE COURT: That request is granted. The Court
10:58:10 6 will certify Dr. Heinecke as an expert in lipoprotein and
10:58:14 7 lipo -- what was the disorder?

10:58:16 8 MR. REIG-PLESSIS: Lipoprotein metabolism and
10:58:19 9 lipid disorders, Your Honor.

10:58:20 10 THE COURT: So granted.

10:58:21 11 MR. REIG-PLESSIS: Thank you.

10:58:22 12 THE WITNESS: It's a mouthful.

10:58:24 13 BY MR. REIG-PLESSIS:

10:58:25 14 Q Dr. Heinecke, do you have slides to assist the Court with
10:58:28 15 your testimony today?

10:58:29 16 A I do.

10:58:32 17 Q So turning to DDX 6.4, could you please summarize the
10:58:40 18 opinions you intend to present today.

10:58:44 19 A Yes. So, in my opinion, all of the asserted claims would
10:58:50 20 have been obvious to a person of ordinary skill in the art as
10:58:54 21 of March 2008.

10:58:56 22 This specifically recites to the claims recited by
10:58:59 23 Amarin as a method purportedly invented of treating a patient
10:59:04 24 with purified EPA comprising a patient population with a
10:59:09 25 triglyceride level of greater than 500 milligrams per

10:59:12 1 deciliter.

10:59:13 2 And let me say this. A lot of the time you see
10:59:15 3 greater than or 499, I tend to just round off there. So
10:59:19 4 greater than or equal to 500 milligrams per deciliter.

10:59:23 5 A duration of therapy of at least 12 weeks.

10:59:26 6 A dosage of the administered medication of 4 grams
10:59:29 7 per day, and a purity of at least 96 percent EPA.

10:59:34 8 And, in my opinion, every element of this method was
10:59:37 9 known in the prior art.

10:59:39 10 Q And turning to DDX 6.5, do you have opinions on whether
10:59:43 11 the prior art would have motivated a person of skill in the
10:59:47 12 art to practice the claimed method of treatment?

10:59:50 13 A I do. I think it would have been obvious because the
10:59:51 14 prior art as of March 2008 taught that Lovaza, a prescription
10:59:59 15 preparation of purified Omega-3 fatty acids, was effective in
11:00:06 16 treating patients with triglycerides greater than 500
11:00:08 17 milligrams per deciliter, but that it had the undesirable side
11:00:10 18 effect of increasing LDL cholesterol, the bad form of
11:00:14 19 cholesterol.

11:00:15 20 It was well established at that time that Lovaza was
11:00:17 21 predominantly composed of EPA and DHA, two Omega-3 fatty
11:00:24 22 acids. It was also known at that time that, unlike DH, 4
11:00:29 23 grams a day of 96 percent pure EPA did not increase LDL
11:00:33 24 cholesterol.

11:00:34 25 So I think it would have been obvious to a person of

1 skill in the art to have tried to use 4 grams a day of at
2 least 96 percent pure EPA to treat patients with triglycerides
3 above 500 milligrams per deciliter to avoid increasing the bad
4 form of cholesterol.

5 Q And turning to DDX 6.6, do you also have opinions on
6 whether the clinical effects recited in certain claims would
7 also have been obvious?

8 A I do. For example, some of the asserted claims
9 specifically require no increase in LDL cholesterol, and my
10 understanding of that is no clinically significant increase in
11 LDL cholesterol;

12 A reduction this triglycerides of at least
13 20 percent;

14 A reduction in apo B, and apo B is the major protein
15 of LDL;

16 No concurrent lipid-altering therapy;

17 And no fatty acid impurity in the EPA preparation of
18 more than 0.6 percent.

19 And, in my opinion, the prior art disclosed all of
20 these requirements providing a reasonable expectation of
21 success.

22 Q Now, which claims did you analyze for your obviousness
23 opinions?

24 A These are listed in the slide shown here. The '929
25 patent, claims 1 and 5, the '728 patent, claims 1 and 16, the

11:01:54 1 '715 patent, claim 14, the '677 patent, claims 1 and 8, the
11:02:02 2 '652 patent, claim 1; and the '560 patent, claims 4 and 17.

11:02:07 3 Q And for the record, since you mentioned the slide, it's
11:02:10 4 DDX 6.7.

11:02:12 5 Turning to DDX 6.8, on the screen are snapshots of
11:02:17 6 the Court's Claim Construction Order, and the parties'
11:02:19 7 stipulation on agreed upon constructions in this case.

11:02:23 8 Did you apply the constructions in these documents
11:02:27 9 in forming your opinions?

11:02:28 10 A To the best of my ability, I did.

11:02:30 11 Q What factors did you consider in forming your opinions on
11:02:36 12 obviousness in this case?

11:02:38 13 A There would be four factors:

11:02:41 14 The level of ordinary skill in the art;

11:02:44 15 The scope and content of the prior art, which I
11:02:47 16 would refer to as the medical literature;

11:02:50 17 The differences between the prior art and the
11:02:53 18 claims; and then

11:02:55 19 Secondary considerations.

11:02:57 20 Q So turning to DDX 6.10, and the first factor of your
11:03:01 21 analysis, how did you define the level of ordinary skill in
11:03:06 22 the art for purposes of the asserted patents?

11:03:09 23 A My definition of an ordinary skill in the art was, first
11:03:14 24 of all, a medical degree or an advanced degree in
11:03:18 25 biochemistry;

1 Secondly, several years of experience developing or
2 using fatty acids to treat lipid disorders, including EPA and
3 DHA, and just to emphasize again that EPA and DHA are specific
4 kinds of fatty acids, called Omega-3 fatty acids.

5 And, finally, access to a team, including a medical
6 doctor, an analytical chemist, or a pharmaceutical chemist.

7 Q So turning now to DDX 6.11, do you understand that Amarin
8 has also proposed a definition for the level of ordinary skill
9 in the art?

10 A I do.

11 Q Do any differences between your definition and Amarin's
12 definition on DDX 6.11 affect your opinions in this case?

13 A I do not believe so.

14 Q Were you a person of skill in the art as of March of 2008
15 under either side's definition?

16 A Yes.

17 Q Do you also have slides analyzing the scope and content
18 of the prior art before March of 2008?

19 A I do.

20 Q Turning to DDX 6.13, what is the prior art that you
21 primarily rely on for your obviousness opinions in this case?

22 A There are four key publications that I rely on. The
23 first is the Lovaza PDR, which we've heard about extensively
24 in prior testimony;

25 The second is Mori, et al., which we've also heard

referred to;

The third is Hayashi; and

The fourth is Kurabayashi.

Q Now, do you also rely on other prior art to provide context for how a person of skill would read these references?

A I do. There's an extensive previous literature supporting our contentions, and I would like to cite some of this literature now.

Q Do you have a timeline to walk through the relevant prior art?

A I do.

Q So turning to DDX 6.14, there is a snapshot on the screen of DX 1527, which is on the parties' admitted exhibit list. Could you identify this document, please.

A Yes. This is a publication from Mochida Pharmaceutical Company describing their Epadel preparation. This is a preparation of highly purified EPA.

Let me mention that there are many different nomenclatures used for EPA, for example, here, they call it ethyl icosapentate. I will just refer to this throughout my presentation as EPA to simplify the understanding.

This describes a preparation of highly purified EPA. And one of the indications at this time, back in 1991, 1992, was already an indication to decrease serum lipids. And they specifically refer here to both triglycerides and cholesterol.

11:06:25 1 Q So turning to DDX 6.15, there is a snapshot of DX 1550,
11:06:32 2 which is also on the parties' admitted list.

11:06:34 3 Could you identify this document, please.

11:06:36 4 A This would be the Takaku publication in 1991. *A Study on*
11:06:43 5 *the Efficacy and Safety of EPA in the Treatment of*
11:06:47 6 *Hyperlipidemia Based on Long-Term Administration Test.* So
11:06:51 7 already, in 1991, there was an interest in testing Epadel for
11:06:56 8 treating lipid disorders.

11:06:59 9 Q And we heard some testimony about it earlier in the week,
11:07:02 10 but does hyperlipidemia include hypertriglyceridemia?

11:07:07 11 A Hyperlipidemia is a broad term. It would include both
11:07:13 12 hypercholesterolemia and hypertriglyceridemia, as well as
11:07:13 13 mixed forms of those disorders, as well as other disorders.

11:07:17 14 Q So now on the screen is DDX 6.16. There is a snapshot of
11:07:23 15 the same exhibit DX 1550, now at page 4.

11:07:28 16 Could you describe the objective of the Takaku 1991
11:07:33 17 study.

11:07:33 18 A Yes. As stated here in the publication itself, they're
11:07:38 19 examining the ability Epadel, a high-purity EPA preparation,
11:07:42 20 to examine its potential safety and usefulness to the
11:07:46 21 treatment of hyperlipidemia.

11:07:52 22 Q And turning to DDX 6.17, which is another snapshot of
11:07:57 23 DX 1550, from pages 12 and 32 of the document, did any of the
11:08:02 24 patients in Takaku have triglycerides above 500?

11:08:07 25 A They did. As shown in Figure 3 on the patient

11:08:12 1 background, in the highlighted column -- excuse me, the
11:08:16 2 highlighted row, there were four subjects that had
11:08:19 3 triglyceride values in the 400 to 1225 range.

11:08:24 4 So clearly, there was at least one subject in the
11:08:27 5 study with a triglyceride value of over 1000 milligrams per
11:08:31 6 deciliter.

11:08:32 7 They give further information on the specifics of
11:08:34 8 this study in Table 11 where they're talking about the shift
11:08:38 9 in serum triglycerides where they note that three of the
11:08:41 10 patients had preadministration values of triglycerides of 650,
11:08:46 11 700, and 1225, in other words, severe hypertriglyceridemia.

11:08:54 12 Note that they also report the effect of the EPA at
11:08:57 13 the end of the treatment interval, which was greater than
11:09:01 14 52 weeks, and in every single subject, except for the subject
11:09:05 15 who had a value of 650 milligrams per deciliter, there was a
11:09:10 16 marked decline in the level of triglycerides.

11:09:12 17 And I'll also point out that at the 40-week point,
11:09:16 18 the one patient who had an initial value of 650 milligrams per
11:09:21 19 deciliter, had a value of 472 milligrams per deciliter on
11:09:26 20 therapy at that time, suggesting that Epadel was significantly
11:09:29 21 lowering triglycerides in this patient population and
11:09:32 22 specifically in patients that had triglycerides above
11:09:36 23 500 milligrams per deciliter.

11:09:38 24 Q So turning now to DDX 6.18, there's another snapshot,
11:09:44 25 again from the same exhibit, DX 1550, now on page 21.

11:09:48 1 Did purified EPA increase LDL cholesterol in the
11:09:53 2 Takaku study?

11:09:54 3 A The authors state that there was no significant
11:09:57 4 fluctuation in the values of serum LDL cholesterol.

11:10:04 5 Q So turning now to DDX 6.19, there is a snapshot on the
11:10:08 6 screen of DX 1551, which is also on the parties' admitted
11:10:13 7 exhibit list. Could you identify this document, please.

11:10:16 8 A Yes. This would be the 1991 Wojenski publication
11:10:22 9 entitled "EPA as an Antithrombotic Agent: Comparison to an
11:10:27 10 Extract of Fish Oil." So already people are considering the
11:10:31 11 comparison of purified EPA to fish oil.

11:10:35 12 Q Turning to DDX 6.20, with a snapshot of DX 1551 from
11:10:43 13 pages 2 and 4, what dosage of purified EPA did Wojenski 1991
11:10:49 14 use?

11:10:50 15 A They were using EPA at a dose of 4 grams per day, and
11:10:55 16 they note that this was greater than 90 percent pure, and they
11:10:59 17 also note that this led to a decrease in serum triglyceride
11:11:03 18 levels of 33 percent; highly statistically significant.

11:11:07 19 Q So according to Wojenski, did 4 grams per day of purified
11:11:12 20 EPA reduce triglycerides?

11:11:14 21 A Yes.

11:11:15 22 Q Now on the screen is DDX 6.21. There's a snapshot of
11:11:21 23 DX 1537 which is also on the parties' admitted exhibit list.
11:11:25 24 Could you identify this document, please.

11:11:27 25 A Yes. This is the 1991 publication of Matsuzawa -- I'm

1 not sure I pronounced that right -- *Effect of Long-Term*
2 *Administration of EPA in Hyperlipidemic Patients.*

3 Q So turning to DDX 6.22, with a snapshot of DX 1537, from
4 pages 1 and 4, what was the product administered in the
5 Matsuzawa 1991 study?

6 A This would be the Epadel preparation of a highly-refined
7 EPA preparation. I would call it highly purified. And the
8 drug was administered for at least 24 weeks, the object being
9 to do so for 52 weeks.

10 Q So did Matsuzawa 1991 teach the administration of
11 purified EPA for at least 12 weeks?

12 A It did.

13 Q Turning now to DDX6.23, there's another snapshot from
14 DX 1537, this time from page 23.

15 Were there any patients in Matsuzawa having a
16 baseline triglyceride level of at least 500?

17 A Yes. As highlighted again in the table, there was at
18 least one patient with a value of above 1000, and given the
19 row above that, where they indicate there was 400 to less than
20 1000 with three patients, it's very likely there were
21 additional patients above 500 milligrams per deciliter.

22 Q Now on the screen is DDX 6.24, with a snapshot of
23 DX 1541, page 3, and DX 1541 is another exhibit on the
24 parties' admitted exhibit list.

25 Could you identify this document, please.

1 A Yes. This would be the 1992 publication in Nozaki,
2 entitled "Effects of Purified EPA on Plasma Lipoproteins in
3 Primary Hypercholesterolemia."

4 Q So turning to DDX 6.25, with a snapshot again from
5 DX 1541, now pages 3 and 6, did the Nozaki 1992 reference
6 provide any background information on EPA?

7 A Yes. They noted, as I previously stated, that fish oil
8 contains a mixture of Omega-3 fatty acids and other fatty
9 acids, including EPA and DHA.

10 They also note that the -- here they call them the
11 n-3 fatty acids, and I would say that that's an alternative
12 nomenclature for Omega-3 fatty acids -- that the n-3 fatty
13 acids consistently reduced serum triglyceride levels.

14 And, "Furthermore," they note, it has been
15 "suggested that EPA and DHA have different properties against
16 lipoprotein metabolism," the obvious possibilities being
17 differences in their effects on triglycerides and LDL and HDL
18 cholesterol.

19 Q Turning now to DDX 6.26, with another snapshot from
20 DX 1541, spanning from pages 3 to 4, what was the objective of
21 the Nozaki 1992 study?

22 A I'll quote from their abstract, "We investigated the
23 effects of purified EPA."

24 So, they were specifically examining highly-purified
25 EPA, and they were interested in triacylglycerols, or

1 triglycerides, and low density lipoprotein cholesterol levels.

2 And they note specifically that triglycerides and
3 LDL cholesterol levels were significantly reduced.

4 They also noted that the apolipoprotein B level was
5 significantly reduced, and this is the major protein content
6 of LDL.

7 Q So did Nozaki 1992 teach that purified EPA could reduce
8 apo B levels without increasing LDL cholesterol?

9 A In my opinion, yes.

10 Q Turning now to DDX 6.27, there's snapshot on the screen
11 of DX 1532 which is also on the parties' admitted exhibit
12 list.

13 Could you identify this document, please.

14 A Yes. This is the 1995 publication of Hayashi, *Decreases*
15 *in Plasma Lipid Content and Thrombotic Activity By EPA*
16 *Purified From Fish Oils.*

17 Q So did the Hayashi 1995 reference relate to purified EPA?

18 A Yes, it did.

19 Q Turning now to DDX 6.28, there's a snapshot on the screen
20 of DX 1532, from page 5.

21 What effect did purified EPA have on lipid levels
22 according to the Hayashi 1995 reference?

23 A They noted a significant reduction in triglycerides of
24 41 percent with no significant -- in their statement, no
25 statistically significant effect on LDL cholesterol levels.

1 And in the table shown here, they document those
2 effects. I'll point out that at baseline, week zero, the
3 triglyceride levels were 300 plus or minus 233.

4 There is a reduction at week 8 to 177 milligrams
5 plus or minus 113, a mean change of 41 percent.

6 I'd also like to point out that there is some
7 ambiguity in this paper about what the meaning is of the plus
8 minus 233. It's not specifically indicated in the paper, but
9 overwhelmingly, in the medical literature, that would be a
10 standard deviation.

11 And that would indicate, just for those of you that
12 are not familiar with the standard deviation definition, a
13 standard deviation is the range of the values it encompasses,
14 the two-thirds middle range of values.

15 So that indicates two things. Because there's a
16 value of plus or minus 233, there was at least one patient in
17 that study who had a value of greater than 300, and because
18 that's only encompassing two-thirds of the data, one-sixth of
19 the patients would likely have been above 533.

20 Now, there is an alternative interpretation that
21 that's the range of the data, although this would be very
22 unusual, and, in that case, there would be at least one
23 patient in the study that had a value of 533.

24 The authors also note that there was no significant
25 change in the LDL cholesterol levels, but the LDL-C definitely

11:18:33 1 did not go up.

11:18:34 2 Q Now, you mentioned that there's two possible
11:18:37 3 interpretations of the 300 plus or minus 233. Under either
11:18:42 4 interpretation, was there at least one patient in Hayashi with
11:18:46 5 triglycerides above 500?

11:18:48 6 A Yes.

11:18:52 7 Q Turning now to DDX 6.29, there's a snapshot of the screen
11:18:59 8 of DX 1530.

11:19:01 9 Could you identify this document.

11:19:04 10 And, for the record, DX 1530 is also on the parties'
11:19:07 11 admitted exhibit list.

11:19:09 12 A This would be the 1997 publication of Grimsgaard,
11:19:14 13 entitled "Highly Purified EPA and DHA in Humans Have Similar
11:19:20 14 Triacylglycerol-Lowering Effects But Divergent Effects on
11:19:24 15 Serum Fatty Acids.

11:19:26 16 Q Now, the title of Grimsgaard 1997 refers to
11:19:31 17 triacylglycerols, is that another term for triglycerides?

11:19:36 18 A Yes, it is.

11:19:39 19 Q So turning to DDX 6.30, which has a snapshot of DX 1530
11:19:46 20 again, now on page 1, what was the objective of the Grimsgaard
11:19:51 21 1997 study?

11:19:53 22 A The objective of this study was to test the possibility
11:19:58 23 that a highly-purified EPA preparation, and a highly-purified
11:20:04 24 preparation of DHA, had differential effects on serum lipids
11:20:11 25 and apolipoproteins.

1 And I would like to highlight the design of this
2 study. This is a double-blind, placebo-controlled, parallel
3 design intervention study. And what that means in simpler
4 terms is they compared three groups of subjects. One group of
5 subjects had had a placebo, so no intervention. One group of
6 subjects that received highly-purified EPA, and one group of
7 subjects that received a highly-purified DHA preparation.

8 The study was carried out with a highly purified
9 form of EPA at 3.8 grams a day, which is very similar to the 4
10 grams a day in the specifications.

11 Q Is 3.8 grams a day about 4 grams per day?

12 A Yes.

13 Q So turning to DDX 6.31, there is a snapshot again from
14 DX 1530, blown-up from page 5 of the document.

15 What effects did about 4 grams per day of purified
16 EPA have on lipid levels in the Grimsgaard 1997 study?

17 A The highly-purified EPA led to a significant decrease in
18 triglycerides. It led to a significant decrease in apo B, and
19 although not significant, a decrease in LDL cholesterol.

20 And let me point out that this table may be
21 confusing because the numbers look different from what we've
22 seen in the past. This is because they're using what are
23 called SI units, which are the units used in Europe and Japan,
24 which have different absolute values from the triglyceride
25 values as they're expressed in the United States.

11:21:51 1 Q And, for the record, what is that unit of measurement
11:21:55 2 that they use in this paper?

11:21:56 3 A That would be the millimoles per liter, which is a
11:22:01 4 concentration measurement.

11:22:03 5 Q Now, in the Grimsgaard 1997 paper, did about 4 grams per
11:22:07 6 day of purified EPA have a significant effect on apo B levels?

11:22:13 7 A It did. It had a 3 percent significant reduction.

11:22:18 8 Q And how do you know that?

11:22:19 9 A They indicate that in the table. There's little 5
11:22:23 10 superscript next to the apo B under the column where they had
11:22:28 11 the EPA treated patients.

11:22:29 12 Q And what does that superscript refer to?

11:22:32 13 A It refers to the P less than .05 at the bottom of the
11:22:38 14 table that's highlighted.

11:22:39 15 Q Does that indicate statistical significance for the
11:22:43 16 result?

11:22:43 17 A It does.

11:22:43 18 Q What was the change in the apo B levels?

11:22:46 19 A About minus 3 percent.

11:22:48 20 Q So what would Grimsgaard 1997 have taught a person of
11:22:52 21 skill in the art about purified EPA?

11:22:55 22 A That purified EPA would lower triglycerides
11:22:59 23 significantly;

11:23:00 24 That purified EPA would not increase LDL
11:23:03 25 cholesterol, and may, in fact, decreased it, although that

change was not significant;

And that it could induce a significant 3 percent reduction in apo B levels.

Q And what was the number of patients in the Grimsgaard 1997 study?

A There was approximately 70 to 75 subjects in each group. So this was a very large study.

Q And we heard about the MARINE study in earlier testimony over the past couple of days. Is this a similar number of patients as Amarin's MARINE study?

A It is. I believe this were approximately 75 subjects in each limb of that study as well.

Q So turning now to DDX 6.32, there is a snapshot on the screen of DX 1531 -- which is also on the parties' admitted exhibit list -- could you identify this document, please.

A Yes. This is the 1997 publication of Harris, entitled "Safety and Efficacy of Omacor in Severe Hypertriglyceridemia."

Omacor is another tradename for Lovaza, which is the prescription drug preparation of highly-purified Omega-3 fatty acids, predominantly DHA and EPA.

Q Was Omacor later renamed to Lovaza then?

A I'm not aware of that, but they are describing the same product.

Q So turning to DDX 6.33, there is another snapshot from DX

1531 at page 1.

Did the Harris 1997 paper describe the contents of Lovaza or Omacor?

A It did. It mentioned that it's containing a high concentration of EPA, approximately 48 percent; and DHA, approximately 38 percent. They also note that it's under investigation.

They use this drug to investigate the triglyceride concentrations in patients with levels between 5.65 and 22.60. These are the different units that I mentioned earlier that are used in Europe and Japan. That would correspond to 500 and 2000 milligrams per deciliter. So all of these subjects had triglycerides of greater than 500.

The drug was used at a dose of 4 grams a day for four months. So it taught the use of this dose in treating patients.

Q Now --

A And I guess I can continue here.

So Omacor significantly reduced the plasma triglyceride concentrations by 45 percent. It also increased the low density lipoprotein cholesterol by 31 percent, and this, again, is the undesirable effect that we see with a mixture of Omega-3 fatty acids when treating triglycerides greater than 500.

So, this is another example of another study that

11:26:03 1 shows the side effect of this intervention.

11:26:05 2 Q So, did Harris 1997 show a particular effect of the
11:26:09 3 combination of EPA and DHA on LDL-C levels?

11:26:13 4 A It did. It showed the that the combination lowered
11:26:16 5 triglycerides very significantly, but increased low density
11:26:20 6 lipoprotein very significantly.

11:26:21 7 Q And would that increase in LDL cholesterol have been
11:26:24 8 desirable?

11:26:25 9 A No.

11:26:28 10 Q So turning to DDX 6.34, there's a snapshot on the screen
11:26:33 11 of DX 1546. Could you identify this document.

11:26:37 12 A This is the 1998 publication of Saito, entitled "Results
11:26:43 13 of Clinical Use of an Improved Formulation of Epadel With
11:26:47 14 Respect to Hyperlipidemia." Again, Epadel would be
11:26:57 15 highly-purified EPA.

11:27:00 16 MR. REIG-PLESSIS: Defendants move the admission
11:27:01 17 of DX 1546.

11:27:04 18 MR. SIPES: No objection, Your Honor.

11:27:05 19 THE COURT: 1546 is admitted.

11:27:05 20 (Defendants' Exhibit 1546 received in
11:27:09 evidence.)

11:27:09 21 BY MR. REIG-PLESSIS:

11:27:12 22 Q So now on the screen is DDX 6.35, with another snapshot
11:27:17 23 of DX 1546 from pages 1, 4, and 14.

11:27:23 24 Was the EPA administered in Saito purified?

11:27:27 25 A Yes. They state that it was of high-purity EPA.

11:27:31 1 Q And according to the Saito 1998 reference, did any
11:27:35 2 patients who took purified EPA have baseline triglycerides
11:27:39 3 above 500?

11:27:40 4 A Yes. According to this study, there was one patient who
11:27:44 5 had a triglyceride value between 500 and 513.

11:27:51 6 Q So turning to DDX 6.36, there is a snapshot of DX 1539,
11:27:58 7 which is on the parties' admitted exhibit list, could you
11:28:02 8 identify this document?

11:28:03 9 A Yes. This is the 1999 publication of Nakamura, et al.,
11:28:08 10 entitled, "Joint Effects of HMG-CoA Reductase Inhibitors and
11:28:08 11 EPA on Serum Lipid Profiles."

11:28:17 12 HMG-CoA reductase inhibitors are the chemical name
11:28:22 13 for the statin family. These are the drugs that are widely
11:28:25 14 used to lower LDL cholesterol.

11:28:28 15 Q So turning to DDX 6.37, with a snapshot, again, of
11:28:34 16 DX 1539 from page 2, was the EPA administered in the Nakamura
11:28:40 17 study purified?

11:28:42 18 A The authors state it was highly-purified EPA.

11:28:46 19 Q And was it administered to patients with hyperlipidemia?

11:28:49 20 A They note in Table 1 that there was a patient with a
11:28:53 21 triglyceride level of 6.31. This is in the international
11:28:57 22 units of millimole per liter. And if we convert that into
11:29:03 23 milligrams per deciliter, that would be approximately
11:29:04 24 560 milligrams per deciliter.

11:29:06 25 Q So is Nakamura 1999 another reference that taught the

11:29:11 1 administration of purified EPA to patients with baseline
11:29:15 2 triglycerides above 500?

11:29:16 3 A Yes.

11:29:17 4 Q Turning now to DDX 6.38, there is a snapshot of DX 1534.
11:29:26 5 Could you identify this document.

11:29:27 6 And, for the record, DX 1534 is also on the parties'
11:29:32 7 admitted exhibit list.

11:29:34 8 A This would be the 2000 publication of Kurabayashi,
11:29:38 9 entitled, "EPA Effect on Hyperlipidemia in Menopausal Japanese
11:29:44 10 Women."

11:29:45 11 Q So now on the screen is DDX 6.39, with another snapshot
11:29:51 12 of DX 1534, from pages 1 and 2.

11:29:55 13 What was the design of the Kurabayashi 2000
11:29:59 14 reference?

11:30:00 15 A This was a 48-week study. It was carried out in
11:30:05 16 hyperlipidemic menopausal women. They randomly assigned 141
11:30:11 17 women to treatment, and the treatment groups were estriol or,
11:30:17 18 excuse me, E3, or EPA.

11:30:22 19 And -- excuse me. Let me start over again with
11:30:25 20 that.

11:30:25 21 So there were two groups. One group of the women
11:30:27 22 was treated with estriol, that's an estrogen.

11:30:31 23 The other group was treated with the estrogen plus
11:30:34 24 EPA, and the drug administered in the study was the
11:30:40 25 highly-purified EPA preparation Epadel which at that time was

over 96.5 percent pure.

Q So turning to DDX 6.40, there's another snapshot of DX 1534, this time at page 3.

What did the combination of estriol in purified EPA have on triglycerides in Kurabayashi?

A The triglycerides were decreased significantly by 27 percent in the EPA treated group. But they increased slightly in the control group that received estriol alone.

And I should, perhaps, point out several things about this study. First of all, estriol is used in menopausal women to relieve the symptoms of menopause, but it's also known to elevate triglyceride levels.

So what we're seeing here in this study is that under these conditions where the patients are actually getting a drug that increased estrogen levels, the EPA is significantly reducing that increase.

They also note that the LDL cholesterol levels, the bad form of cholesterol, decreased significantly in both groups. So there was no increase in LDL cholesterol in this study in the EPA treated group.

Q Do these results suggest any interaction or synergy between estriol and EPA?

A Actually not. Synergy is usually seen between drugs that have similar effects.

For example, if you combine two drugs that reduce

1 blood pressure together, you typically get a better blood
2 pressure reduction.

3 But as I just alluded to, estrogen or estriol
4 typically increases estrogen levels, and so the fact that
5 we're seeing this effect argues against the hypothesis that
6 synergy is occurring.

7 Now, of course, one can never exclude the
8 possibility there might be some unknown synergy. But that
9 would not be very likely under these circumstances.

10 Q And just so the record is clear, I think you said estriol
11 increases estrogen levels?

12 A Excuse me. It mimics an increase in estrogen levels. So
13 what you're trying to do here is to replace the estrogen
14 that's been lost as the women go through menopause.

15 Q Were the results in Kurabayashi seen in patients with
16 hypertriglyceridemia?

17 A Yes.

18 Q How do you know that?

19 A Wait. Restate the question here again, please?

20 Q Sure.

21 Were the results in Kurabayashi seen in patients who
22 had triglyceride levels that were above normal?

23 A Yes. It states here that the patients have an increase
24 from 192 milligrams per deciliter, so that would be greater
25 than 150 milligrams per deciliter.

Q So turning to DDX 6.41, there is a snapshot again of DX 1534, now pages 3 and 5.

Did Kurabayashi report any changes in apo B levels in patients taking purified EPA?

A They did. They state that the apolipoprotein B level in the EPA group was significantly lower at week 48. They have those results shown in the table.

What we're looking at here is the percent change in apo B at week 48, and what is found is that there is a nonsignificant change in the control group of minus 1.5 percent, and a highly significant change, a decrease, in the EPA group of 6.9 percent. The P value there is less than .001. That's very significant.

And this was -- the analysis in this study was carried out by the one way repeated analysis of variance.

So I might mention one of the advantages of this study is that they had multiple determinations of the apo B levels over the course of the study, and so they were able to use all of those in concert to determine the change in the apo B levels.

And this is a more powerful approach than simply measuring the values at the beginning and the end of the study.

Q Now, based on these data, would a person of skill in the art have attributed the reduction in apo B to the estriol or

11:35:02 1 to the EPA in Kurabayashi?

11:35:03 2 A The EPA therapy.

11:35:05 3 Q And why is that?

11:35:06 4 A Because a control group had a nonsignificant decrease in
11:35:13 5 apo B, and the addition of EPA led to a significant decrease
11:35:18 6 in apo B levels.

11:35:21 7 So in this study design that would indicate that the
11:35:24 8 effect was due to the EPA treatment.

11:35:26 9 Q And turning to DDX 6.42, which has snapshots from DX 1541
11:35:33 10 and DX 1530, was the reduction in apo B observed in
11:35:39 11 Kurabayashi consistent with earlier studies on EPA that we've
11:35:43 12 discussed?

11:35:43 13 A It was. It was consistent with Nozaki, et al., 1992,
11:35:47 14 where there was a significant reduction in apo B, and in
11:35:52 15 Grimsgaard 1997, where there was likewise a 3 percent
11:35:55 16 significant reduction in apo B levels in the EPA treated
11:36:00 17 groups.

11:36:00 18 Q Was estriol administered to patients in these studies?

11:36:06 19 A It was not.

11:36:09 20 Q Would a person of skill in the art in March of 2008 have
11:36:10 21 been aware of Nozaki and Grimsgaard when interpreting the
11:36:12 22 results of Kurabayashi?

11:36:13 23 A Taken together, I believe that these three studies
11:36:16 24 provide very strong evidence that apo B levels can in fact be
11:36:21 25 lowered by EPA therapy.

Q So turning to DDX 6.43, there's a snapshot of DX 1538, which is also on the parties' admitted exhibit list.

Could you identify this document for the record.

A Yes. This is the 2000 publication of Mori, entitled "Purified EPA and DHA Have Differential Effects on Serum Lipids and Lipoproteins."

Q Now, turning to DDX 6.44, there is another snapshot of the Mori study, which is DX 1538, from pages 1 to 2.

What was the objective of the Mori 2000 study?

A The objective was to determine whether EPA -- and they say "and," but I would say "or DHA" -- have differential effects on serum lipids and lipoproteins.

It was a double-blind, placebo-controlled trial. That means that the investigators were not aware of the intervention, that they used two interventions, and they compared the effects of those interventions with a group that received no therapy, a placebo group.

The treatment was 4 grams of purified EPA a day, or purified DHA. And I'll note that none of the subjects were regularly taking lipid-lowering drugs, or other drugs known to a lipid -- known to affect lipid metabolism.

Q So were any of the patients in Mori 2000 taking concurrent lipid-altering therapy?

A No, they were not, and that would include the estriol or other estrogenic drugs.

11:38:00 1 Q So turning to DDX 6.45, with another snapshot of DX 1538,
11:38:06 2 this time from pages 2 to 3, what was the purity of EPA used
11:38:11 3 in the Mori 2000 study?

11:38:14 4 A They note that it was approximately 96 percent pure, and,
11:38:17 5 again, it was given at a dose of 4 grams a day.

11:38:20 6 Q And according to Mori, what were the effects of 4 grams a
11:38:26 7 day of purified EPA and purified DHA on lipid levels?

11:38:31 8 A Again, they observed a significant reduction in -- here
11:38:35 9 they call them triacylglycerols, but that's triglycerides --
11:38:40 10 of 18.4 percent with EPA and 20 percent with DHA.

11:38:44 11 In my opinion, the difference between 18 percent and
11:38:49 12 20 percent reduction is indistinguishable and of no clinical
11:38:49 13 significance.

11:38:53 14 They also note that LDL cholesterol increased
11:38:57 15 significantly with DHA, by 8 percent, but not with EPA,
11:39:02 16 strongly suggesting that these two Omega-3 fatty acids could
11:39:06 17 have distinct effects on LDL cholesterol levels.

11:39:09 18 Q Now, does the 3.5 percent higher value for EPA indicate
11:39:14 19 that there was an increase in LDL-C levels for the EPA group?

11:39:18 20 A No, it does not, and I think this comes back to trying to
11:39:22 21 understand what the significance of changes is in terms of
11:39:25 22 statistical testing.

11:39:27 23 If one repeatedly measures a variable over and over
11:39:30 24 again, there will always been variation, and so by chance
11:39:34 25 alone you can have a small increase or decrease.

1 The way one assesses a significance of a change is
2 by making the assumption that it is different from chance.

3 And so this is a key concept. I think it's very
4 important to realize that small variations around the mean do
5 not mean that those are necessarily significantly different.

6 Q So turning now to DDX 6.46, there's a snapshot of DX 1526
7 which is also on the parties' admitted exhibit list.

8 Could you identify this document, please.

9 A Yes. This is the 2001 ATP III expert guidelines. We've
10 heard about this repeatedly over the last several days.

11 This is a treatment panel recommendation for how to
12 focus detection and treatment of high blood cholesterol in
13 adults, and I plan to summarize something here from the
14 executive summary.

15 Q Turning to DDX 6.47, with a snapshot of page 11 from
16 DX 1526, what was the main treatment goal identified by
17 ATP III?

18 A The main treatment goal identified in ATP III was LDL
19 cholesterol, and this has been a longstanding recommendation,
20 and ATP III was one of the first publications that put the
21 emphasis here.

22 This reflects the fact that elevated LDL cholesterol
23 was a major cause of coronary heart disease, and I might
24 mention many, many different lines of evidence support this.

25 For example, in familial hypercholesterolemia, which

1 is a disorder of the LDL receptor, a protein that breaks down
2 LDL, patients who lack both copies of this gene can have heart
3 attacks before the age of 10. They have enormously elevated
4 levels of LDL cholesterol and they suffer from very strong
5 premature coronary artery disease.

6 Moreover, there are now many -- and at that time
7 there were many, many trials showing that lowering LDL
8 cholesterol produced cardiovascular benefit.

9 And ATP III really just formalizes this data into
10 one treatment panel recommendation. They also take into
11 consideration a number of other factors, and relate those to
12 the significance of LDL cholesterol.

13 Q So now on the screen is DDX 6.48. It's a snapshot of
14 DX 1552, which is also on the parties' admitted exhibit list.
15 Could you identify this document.

16 A Yes. This is the 2003 publication of Yokoyama, et al.,
17 entitled "Effects of EPA on Cardiovascular Events in Japanese
18 Patients: Rationale, Design, and Baseline Characteristics of
19 the Japan EPA Lipid intervention Study."

20 This is the JELIS trial that we've heard about
21 previously.

22 This is not a description of the study results
23 itself. This is a prespecified outline of what the analyses
24 for that trial will be and how it will be carried out, and
25 this is very, very important because it indicates specifically

1 how the study will be carried out and how the data will be
2 analyzed.

3 And this circumvents issues related to things like
4 data dredging where people try to change the way they do the
5 analysis to interpret the significance of the results.

6 I'll also point out that this is in 2003.
7 Investigators were already interested in the idea that EPA
8 might reduce cardiovascular risk.

9 Q So turning to DDX 6.49, there is another snapshot from
10 DX 1552, now from pages 3 to 4.

11 What was the specific product used in the JELIS
12 trial?

13 A This, again, would be the Epadel capsules containing
14 highly-purified EPA.

15 Note that now it's greater than 98 percent pure, and
16 this indicates that Mochida was continuously trying to improve
17 the purity of their product and to yield something that was
18 even more highly purified than in the initial Mochida
19 description that I described back in 1991.

20 The Epadel capsules were launched in 1990, as I just
21 mentioned, and this is an even more highly-purified form of
22 EPA.

23 Q By 2003, was the Epadel product indicated to treat
24 hyperlipidemia?

25 A It was.

11:44:06 1 Q And does hyperlipidemia include an excess of
11:44:11 2 triglycerides?

11:44:12 3 A It does.

11:44:12 4 Q So turning now to DDX 6.50, there is a snapshot from
11:44:21 5 DX 1536, also on the parties' admitted exhibit list.

11:44:25 6 Could you identify this document, please.

11:44:27 7 A Yes. This is the 2005 Maki publication, entitled "Lipid
11:44:33 8 Responses to Dietary DHA." So this is the other major
11:44:37 9 component of fish oil, DHA.

11:44:43 10 Q So now on the screen is DDX 6.51 with another snapshot
11:44:48 11 from DX 1536 from pages 1 and 9.

11:44:52 12 What effect did DHA have on LDL cholesterol in Maki
11:44:57 13 2005?

11:44:58 14 A They found that it raised LDL cholesterol levels, and
11:45:02 15 they noted in the discussion of this paper that most previous
11:45:06 16 studies of DHA supplementation had shown increases in LDL
11:45:10 17 cholesterol.

11:45:11 18 And one of the things I like about this paper is
11:45:13 19 they note that there's always a range of responses. So they
11:45:16 20 specifically say that there is was a range of decrease of 3
11:45:21 21 percent to an increase of 16 percent in LDL cholesterol
11:45:25 22 levels, but that the median was 7.2 percent.

11:45:28 23 And so what they're addressing here is all clinical
11:45:31 24 studies have somewhat different results, and they're trying to
11:45:34 25 give a feel for the range in the variation in those results.

1 So, in my opinion, this provides very strong
2 evidence that DHA, one of the two components of Lovaza, or
3 highly-purified fish oil, is very likely responsible for the
4 increase in LDL cholesterol levels.

5 Q And is that in contrast with the EPA component of fish
6 oil or Lovaza?

7 A Yes. In my opinion, when I take the data as a whole, it
8 strongly suggests that EPA is lipid neutral with respect to
9 LDL cholesterol, or perhaps can even lower LDL cholesterol.

10 Q So turning to DDX 6.52, there's a snapshot now of
11 DX 1535, also on the parties' admitted exhibit list.

12 Could you identify this document?

13 A Yes. This is the -- excuse me here.

14 This is the Lovaza PDR insert 2007. The PDR is the
15 *Physicians' Desk Reference*. This is a publication that
16 summarizes the treatment and recommendations for drugs that
17 have been approved by the FDA for treating various disorders.

18 Q And do you understand that although this label is from
19 2007, in the 2008 edition of the PDR, that Lovaza was first
20 commercially launched in 2004?

21 A Yes, I'm aware of that.

22 Q So turning to DDX 6.53, with another snapshot of DX 1535,
23 now from pages 2 to 3.

24 Is Lovaza the same as Omacor that was discussed in
25 the Harris 1997 paper we reviewed earlier?

11:47:17 1 A Yes, it is.

11:47:18 2 And I might mention that Lovaza is here described as
11:47:23 3 a mixture of EPA and DHA, as I previously emphasized, and that
11:47:27 4 it's indicated as an adjunct to reduce triglyceride levels in
11:47:31 5 adult patients with very high triglyceride levels, here
11:47:35 6 defined as greater than or equal to 500 milligrams per
11:47:39 7 deciliter.

11:47:39 8 Q Is that the same indication that we've heard testimony
11:47:42 9 about earlier with respect to Vascepa?

11:47:45 10 A Yes, it is.

11:47:46 11 Q So turning now to DDX 6.54, there's another snapshot from
11:47:54 12 DX 1535, page 2. What was the indicated dosage for Lovaza?

11:48:00 13 A The indicated dosage was 4 grams per-day administered by
11:48:04 14 mouth, or here it's "oral administration."

11:48:07 15 Q Did the Lovaza PDR discuss any clinical studies on
11:48:13 16 Lovaza?

11:48:13 17 A They specifically site a study of 16 weeks duration at 4
11:48:18 18 grams per day of Lovaza. So this would be greater than
11:48:21 19 12 weeks.

11:48:22 20 Q Turning now to DDX 6.55, with another snapshot from
11:48:29 21 DX 1535, now page 3, what effect did Lovaza have on LDL
11:48:35 22 cholesterol according to the Lovaza PDR from 2007?

11:48:43 23 A Well, we've seen this slide several times before, but
11:48:46 24 just to reiterate, what they observed was a very significant
11:48:46 25 increase in the LDL cholesterol in the Lovaza treated group of

11:48:50 1 about 49 percent compared with placebo-controlled.

11:48:54 2 Q Would a person of skill in the art have been motivated to
11:48:58 3 avoid that increase in LDL-C?

11:49:01 4 A Yes.

11:49:04 5 Q So turning now to DDX 6.56, there is a snapshot on the
11:49:09 6 screen of DX 1528, also on the parties' admitted exhibit
11:49:14 7 list.

11:49:14 8 Could you identify this document, please.

11:49:16 9 A Yes. This would be another publication from Mochida
11:49:21 10 Pharmaceutical, the company that originally developed Epadel
11:49:24 11 in the early '90s, and they're now describing a new
11:49:27 12 formulation of that that became available in 19 -- excuse me,
11:49:32 13 in 2007.

11:49:35 14 Q So is this an updated version of the Epadel labeling from
11:49:40 15 1991 that we looked at earlier?

11:49:43 16 A Yes, it is.

11:49:43 17 Q Turning to DDX 6.57, there's another snapshot from
11:49:48 18 DX 1528, now at page 2.

11:49:50 19 As of 2007, was Epadel indicated to reduce
11:49:57 20 triglycerides?

11:49:57 21 A It is. And I'll note that this is in contrast to the
11:50:00 22 original description in '91 which simply specified
11:50:04 23 hyperlipidemia. They're now specifically referring to an
11:50:08 24 excess of triglycerides.

11:50:08 25 Q Was there any upper limit to the excess of triglycerides

11:50:11 1 that Epadel was indicated to treat?

11:50:14 2 A Nothing specific is indicated here.

11:50:16 3 Q So did the indication for Epadel in 2007 include patients
11:50:21 4 with triglycerides above 500?

11:50:22 5 A Yes, it did.

11:50:23 6 Q Was there any warning on the Epadel label about increases
11:50:29 7 in LDL-C similar to the warning we saw in the Lovaza label?

11:50:32 8 A No, there is not.

11:50:34 9 Q So turning now to DDX 6.58, there is a snapshot from
11:50:41 10 DX 1553, also on the parties' admitted exhibit list.

11:50:45 11 Could you identify this document.

11:50:46 12 A Yes. This is actually reporting the results of that
11:50:51 13 earlier publication from Yokoyama, et al., and it's entitled
11:50:55 14 "The Effects of EPA on Major Coronary Events and
11:51:00 15 Hypercholesterolemic Patients, A Randomized Open-Label,
11:51:04 16 Blinded Endpoint Analysis."

11:51:06 17 This is also known as the JELIS study published in
11:51:09 18 *The Lancet* in 2007.

11:51:12 19 *The Lancet*, along with *The New England Journal of*
11:51:16 20 *Medicine*, are considered two of the most prestigious journals
11:51:19 21 in clinical medicine.

11:51:21 22 Q So what's the difference between the Yokoyama 2007 paper
11:51:24 23 we have on the screen and the Yokoyama 2003 paper we discussed
11:51:28 24 earlier?

11:51:28 25 A The earlier paper described the study design, and, even

1 more importantly, exactly how the data would be analyzed.

2 This study is reporting the results of that.

3 Q So turning to DDX 6.59, with another snapshot from
4 DX 1553, page 1, what were the results of the JELIS study as
5 reported in Yokoyama 2007?

6 A The primary endpoint of the study was any major coronary
7 event, including sudden cardiac death, fatal and non-fatal MI,
8 MI is myocardial infarction or heart attack, and non-fatal
9 events including unstable angio pectoris, that would be chest
10 pain --

11 COURT REPORTER: Slow down.

12 THE WITNESS: I'll start over again. Excuse me.

13 The primary endpoint was any major coronary
14 event, including sudden cardiac death, fatal and non-fatal
15 myocardial infarction, in other words, a heart attack, or
16 other nonfatal events, including unstable angina pectoris,
17 this is where you have occlusion of the blood flow and chest
18 pain, stenting, which is a treatment for an occluded artery,
19 or coronary artery bypass grafting, another treatment for an
20 occluded artery supplying blood to the heart.

21 And the really, the remarkable findings of this
22 study -- and let me make one other very important point. All
23 of these patients were on statin therapy. So all of these
24 patients were receiving the best known therapy for preventing
25 heart disease at this time.

11:53:06 1 There was a remarkable 19 percent relative
11:53:10 2 reduction in major coronary events in this study.

11:53:14 3 And in the author's note in the discussion,
11:53:17 4 "EPA is a promising treatment for the
11:53:19 5 prevention of major coronary events."

11:53:25 6 Q So turning to DDX 6.60, on the screen is a snapshot of
11:53:30 7 DX 1524. Could you identify this document.

11:53:34 8 A Yes. This is another document from Mochida, an
11:53:38 9 international patent application that was published in 2007,
11:53:42 10 and it's referred to as WO '118.

11:53:46 11 MR. REIG-PLESSIS: Defendants' move the
11:53:47 12 admission of DX 1524 into evidence.

11:53:50 13 MR. SIPES: No objection, Your Honor.

11:53:51 14 THE COURT: 1524 is admitted.

11:53:51 15 (Defendants' Exhibit 1524 received in
11:53:54 evidence.)

11:53:54 16 BY MR. REIG-PLESSIS:

11:54:05 17 Q So turning now to DDX 6.61, with another snapshot from
11:54:10 18 DX 1524 from pages 25 and 35, according to WO '118, was Epadel
11:54:18 19 commercially available in 2007?

11:54:21 20 A Yes, it was. They describe it as a capsule containing
11:54:25 21 high-purity EPA. They note that it's commercially available,
11:54:29 22 that it is a safe therapeutic agent for hyperlipidemia, and
11:54:35 23 that the proportion of EPA in the preparation is at least
11:54:40 24 96.5 percent weight.

11:54:41 25 They also specifically note that the daily dose of

11:54:44 1 EPA is typically 0.3 to 6 grams a day, but preferably 0.9 to
11:54:53 2 3.6 grams a day.

11:54:54 3 And, again, I'll point out that 3.6 grams a day is,
11:54:57 4 in my opinion, indistinguishable from 4 grams a day.

11:55:03 5 Q So turning to DDX 6.62, there is a snapshot of DX 1525.
11:55:09 6 Could you identify this document.

11:55:10 7 A Yes. This is another publication for an international
11:55:15 8 patent WO '900, and here referred to as WO '900 for the
11:55:23 9 production of ultrapure EPA.

11:55:28 10 Q And I'll just note for the record DX 1525 is also on the
11:55:32 11 parties' admitted exhibit list.

11:55:34 12 So turning to DDX 6.63, there's another snapshot of
11:55:39 13 the same exhibit, DX 1525, from pages 6 and 17.

11:55:45 14 What level of purity of EPA could be achieved with
11:55:49 15 the purification method disclosed in WO '900?

11:55:52 16 A They state the composition comprises between 99.6 and
11:55:59 17 99.9 percent EPA. In other words, there was less than
11:56:08 18 0.4 percent impurity in this preparation, and they
11:56:12 19 specifically note that there was less than 0.1 percent of DHA
11:56:16 20 in this preparation, and that would be the other major
11:56:19 21 component of purified Lovaza.

11:56:22 22 Q Now, is there additional prior art that Amarin has relied
11:56:27 23 on in this case besides the prior art in your timeline?

11:56:30 24 A There is.

11:56:31 25 Q And do you have slides later in your presentation

11:56:34 1 addressing some of those references?

11:56:36 2 A I do.

11:56:36 3 Q Now, do you understand that the examiner who issued
11:56:41 4 Amarin's patents had access to the key prior art in your
11:56:44 5 timeline?

11:56:45 6 A I do.

11:56:45 7 Q Have you reviewed the prosecution history of the asserted
11:56:49 8 patents?

11:56:50 9 A I have.

11:56:51 10 Q So turning now to DDX 6.64, there's snapshot of DX 1595,
11:57:04 11 which has been admitted into evidence, from pages 8 and 9.

11:57:09 12 In deciding to issue the patents in this case, was
11:57:12 13 there a limitation of the claims that the examiner believed
11:57:16 14 was not described in the prior art?

11:57:18 15 A There was. This is the Notice of Allowance, September 6,
11:57:25 16 2012, and the examiner notes,

11:57:27 17 "The prior art does not teach the
11:57:29 18 administration of EPA to patients having triglyceride
11:57:33 19 levels between 500 and 1500 milligrams per
11:57:38 20 deciliter," and notes, "as such, there is no
11:57:40 21 anticipation."

11:57:46 22 Q Now, turning to DDX 6.66, do you agree with the
11:57:51 23 examiner's finding about the prior art in the Notice of
11:57:55 24 Allowance?

11:57:55 25 A I do not. I've cited multiple publications that indicate

1 that this had been tried previously, including the Hayashi
2 publication in 1995 where there was clearly at least one
3 patient with a triglyceride value of greater than 500, and if
4 that is, in fact, a standard deviation, there were many more
5 than that, perhaps as many as four or five.

6 There's the Saito publication of 1998 where there is
7 one patient with a value above 500.

8 There's the Takaku patient paper in 1991 where there
9 were three patients with triglycerides greater than 500,
10 specifically 650, 700 and 1225.

11 The Matsuzawa paper in 1991 with one patient with a
12 value of 1510.

13 And the Nakamura paper, 1999, with one patient who
14 had a triglyceride level of approximately 560 milligrams per
15 deciliter.

16 Q And turning now to DDX 6.67, do you recognize DX 1588 as
17 the examiner's nonfinal rejection from March 2, 2012?

18 A Yes.

19 MR. REIG-PLESSIS: Defendants' move the
20 admission to DX 1588.

21 MR. SIPES: No objection, Your Honor.

22 THE COURT: 1588 is admitted.

23 (Defendants' Exhibit 1588 received in
24 evidence.)

25 BY MR. REIG-PLESSIS:

Q Now, prior to the Notice of Allowance that just reviewed,

1 did the examiner originally have a different view of the prior
2 art?

3 A They did. Specifically, they say that,
4 "Hayashi teaches that the administration of
5 EPA to individuals with serum triglyceride levels of
6 300, plus or minus 233 milligrams per deciliter,
7 i.e., between 67 and 533 milligrams per deciliter,
8 for eight weeks caused a decrease in serum
9 triglycerides of about 41 percent."

10 Q So did the examiner originally believe that Hayashi
11 disclosed the administration of EPA to patients with
12 triglycerides above 500?

13 A Based on this statement, yes.

14 Q Now, turning to DDX 6.68, do you recognize this as -- I'm
15 sorry. There is a snapshot from DX 1598 -- 1589, excuse me,
16 page 2.

17 Do you recognize this as Amarin's response to the
18 nonfinal rejection that we just reviewed?

19 A Yes. This was the declaration of Philip Lavin, a
20 statistician who was asked to evaluate the significance of the
21 values in the Hayashi paper.

22 And he states,
23 "Given this interpretation, the one-sided
24 99.9 percent upper confidence bound in the Hayashi
25 population is 450 milligrams per deciliter."

12:00:51 1 And then goes on to state, "This means that
12:00:54 2 not even one patient in the study would be expected
12:00:57 3 to have a triglyceride level of 450 milligrams per
12:01:02 4 deciliter or higher."

12:01:05 5 MR. REIG-PLESSIS: And defendants move the
12:01:05 6 admission of DX 1589 into evidence.

12:01:09 7 MR. SIPES: No objection, Your Honor.

12:01:10 8 THE COURT: 1589 is admitted.

12:01:10 9 (Defendants' Exhibit 1589 received in
12:01:13 10 evidence.)

12:01:13 10 BY MR. REIG-PLESSIS:

12:01:14 11 Q So turning to DDX 6.69, since that declaration we just
12:01:18 12 reviewed, has Dr. Lavin acknowledged that he made a mistake
12:01:23 13 about the Hayashi paper?

12:01:25 14 A Yes. Dr. Lavin was deposed specifically with regard
12:01:29 15 regards to this statement, and he said -- he says in, his own
12:01:33 16 words,

12:01:34 17 "It is likely that you have at least one or
12:01:36 18 two observations above 533. It isn't zero. Let's go
12:01:42 19 on record there, it is not zero....you know that
12:01:46 20 there must be at least one subject."

12:01:50 21 And the examiner then asked, "So given that,
12:01:53 22 would you rewrite paragraph 12?"

12:01:55 23 And he answers, "I would."

12:01:57 24 Q And is paragraph 12 the paragraph of Dr. Lavin's
12:02:01 25 declaration that we reviewed on the previous slide, DDX 6.68?

12:02:05 1 A Yes.

12:02:06 2 MR. REIG-PLESSIS: For the record, at DDX 6.69,
12:02:09 3 the snapshot is from Dr. Lavin's deposition at page 103, from
12:02:15 4 lines 11 to 21.

12:02:15 5 BY MR. REIG-PLESSIS:

12:02:20 6 Q Now, turning to DDX 6.70, regardless of whether Dr. Lavin
12:02:25 7 was right about Hayashi, did the examiner overlook other prior
12:02:30 8 art in which purified EPA was given to patients with
12:02:33 9 triglycerides above 500?

12:02:34 10 A Yes. In my opinion, they overlooked four other relevant
12:02:39 11 publications as I previously mentioned: Saito '98, Takaku
12:02:46 12 '91, Matsuzawa '91, Nakamura '99, and, again, I'd like to
12:02:51 13 highlight the Takaku paper which had three patients with
12:02:55 14 values greater than 500 milligrams per deciliter.

12:03:00 15 Q Now, turning to DDX 6.71 --

12:03:04 16 MR. REIG-PLESSIS: And I'll just note, Your
12:03:05 17 Honor, this is a different section if we're considering taking
12:03:10 18 a lunch break. We could also go on further. But, this is a
12:03:14 19 different section that will probably be fairly long.

12:03:23 20 THE COURT: I'm going to try to space the breaks
12:03:25 21 so the afternoon is not too long. My preference is we proceed
12:03:29 22 for another 30 minutes or so.

12:03:31 23 MR. REIG-PLESSIS: That's perfectly fine, Your
12:03:32 24 Honor. I just wanted to let you know that this one will
12:03:34 25 probably be a little long.

12:03:36 1 THE COURT: Thirty minutes long?

12:03:39 2 MR. REIG-PLESSIS: Likely longer than that.

12:03:41 3 THE COURT: Let's proceed.

12:03:43 4 THE WITNESS: I can try and go quickly if that
12:03:45 5 would be --

12:03:45 6 THE COURT: No, that would not be a solution at
12:03:47 7 all.

12:03:47 8 MR. REIG-PLESSIS: I don't think the court
12:03:48 9 reporter would like that.

12:03:49 10 THE COURT: We all need to be able to follow --

12:03:52 11 THE WITNESS: We're all eager to get out of
12:03:55 12 here.

12:03:55 13 BY MR. REIG-PLESSIS:

12:03:55 14 Q Dr. Heinecke, do you have also have slides analyzing the
12:03:58 15 differences between the prior art that we reviewed and the
12:04:01 16 asserted claims?

12:04:02 17 A I do.

12:04:03 18 Q Now, what is the legal standard that you applied in
12:04:09 19 analyzing the differences between the prior art and the
12:04:12 20 claims?

12:04:13 21 A First of all, I want to emphasize I'm not a lawyer, so
12:04:16 22 I'm trying apply my understanding as best I can. I'm not
12:04:20 23 rendering a legal judgment here.

12:04:22 24 But my understanding is the difference between the
12:04:24 25 prior art and a patent claim are obvious when the prior art

discloses each element of the claim, when there's a motivation to combine the disclosed elements to arrive at the claimed invention, and, there's a reasonable expectation of success.

Q Now, turning to DDX 6.73, did the key prior art that you rely on disclose the elements that appear in all of the asserted claims?

A In my opinion, yes.

The first key element is for the patient to have a triglyceride value of greater than or equal to 500 milligrams per deciliter, and I believe the Lovaza and Hayashi publications support this.

The duration of therapy had to be at least 12 weeks, and, again, the Lovaza and the Kurabayashi publications would support this.

The dosage needs to be about 4 grams a day, and, again, Lovaza and Mori.

And, finally, the purity of the preparation of the EPA should be about 96 percent, and Mori and Kurabayashi both use EPA preparations of this purity.

Q And turning to DDX 6.74, did the key prior art that you rely on disclose the remaining elements that appear in only some of the asserted claims?

A Yes. So some of the claims require no increase in LDL cholesterol, and this would be addressed by Mori, Hayashi, and Kurabayashi.

1 There was another requirement for a triglyceride
2 reduction of at least 20 percent, and Hayashi addresses this
3 issue.

4 There was a requirement for an apo B reduction, and
5 Kurabayashi indicates this.

6 No other concomitant lipid-altering therapy, which
7 was addressed in Mori, et al., and no impurity greater than
8 0.6 percent, which would be the woo -- the WO international
9 Patent '900.

10 Q Now, turning to DDX 6.75, could you summarize how a
11 person of skill in the art would have combined the elements in
12 the prior art?

13 A I really think this is pretty simple. The prior art
14 taught that Lovaza, 4 grams a day, would be used to treat
15 patients with triglyceride levels of greater than
16 500 milligrams per deciliter, but that it increased LDL-C. It
17 increased the bad form of cholesterol. We know the two major
18 components of Lovaza are EPA and DHA.

19 Moreover, Mori, et al., demonstrated that unlike
20 DHA, purified EPA, 4 grams a day, reduced triglycerides
21 without increasing LDL cholesterol levels.

22 And it's -- it's obvious to me a clinician
23 interested in this situation would have considered using 4
24 grams of purified EPA to treat patients with triglycerides
25 greater than 500 with the desirable goal of not increasing LDL

cholesterol level.

Q Now, did you also analyze whether using purified EPA to treat patients with triglycerides above 500 was at least obvious to try?

A Yes.

Q And what legal standard did you apply for that analysis?

A My understanding is that there is a design need or market pressure to solve a problem, and so that would be the undesirable increase in LDL cholesterol, and, that there be a finite number of identified predictable solutions to that problem.

Given that Lovaza had two major components, DHA and EPA, there were two very strong possibilities for what one might want to test to see if one or the other or both were the problem at hand.

Q So to a person of skill in the art who was investigating which component of Lovaza was responsible for increasing LDL-C, what were the possible choices?

A Okay. I'll say it again. There was a need to reduce triglycerides in patients with elevated high triglycerides greater than 500 milligrams per deciliter, and we know that Lovaza was indicated for that and was very effective at lowering triglycerides, but that it led to an undesirable increase in LDL cholesterol.

So, the identified and predictable solutions for

12:08:51 1 reducing triglycerides would include using a 4 gram per day
12:08:56 2 dose of a purified EPA, and so the obvious possibilities were
12:09:01 3 it could be EPA that was a problem, it could be DHA that was a
12:09:06 4 problem, it could be both that were a problem, and so that was
12:09:10 5 very obvious to test, in my opinion.

12:09:14 6 Q Let's turn to your analysis of the individual asserted
12:09:18 7 claims. Which claims are you analyzing first?

12:09:21 8 A That would be the '929 patent, claims 1 and 5.

12:09:25 9 Q Turning to DDX 6.79, on the screen is claim 1 of the '929
12:09:34 10 patent. What is the first limitation you analyzed in this
12:09:39 11 claim?

12:09:39 12 A I'm not seeing anything on my screen.

12:09:42 13 Q Oh, My apologies.

12:09:43 14 A This would be the '929 patent, claim 1, the broadest
12:09:47 15 claim,

12:09:47 16 "A method of reducing triglycerides in a
12:09:49 17 subject having fasting triglycerides of at least
12:09:52 18 500 milligrams per deciliter."

12:09:54 19 And it's my belief that the Lovaza PDR taught
12:09:57 20 this, the Lovaza PDR 2007, where they specifically say to use
12:10:01 21 Lovaza to reduce triglycerides in an adult patient with very
12:10:05 22 high triglyceride levels defined here as greater as 500.

12:10:13 23 Q So turning to DDX 6.80, what is the next limitation you
12:10:18 24 analyzed in claim 1 of the '929 patent?

12:10:21 25 A There would be a requirement for oral administration for

1 at least 12 weeks of a pharmaceutical composition.

2 And, again, the Lovaza PDR 2007 teaches this. It
3 specifically states, "oral administration." In one of the
4 studies they cite it was for 16 weeks, so, greater than
5 12 weeks.

6 Q Turning to DDX 6.81, is there any difference between the
7 method disclosed in the Lovaza PDR and the method recited in
8 claim 1 of the '929 patent?

9 A Yes. Lovaza is a mixture of EPA and DHA, and the
10 difference is now they're claiming purified EPA containing no
11 more, or about, 4 percent DHA.

12 Q Was that the only difference between the Lovaza PDR and
13 the claimed method of treatment?

14 A Yes.

15 Q So turning to DDX 6.82, was the limitation requiring 4
16 grams of 96 percent pure EPA taught in any other prior art
17 that you rely on?

18 A It was. Mori 2000 administered 4 grams a day of highly
19 purified EPA, specifically stated to be approximately
20 96 percent pure.

21 Q Were all of the elements in claim 1 of the '929 patent
22 taught by the combination of the Lovaza PDR and Mori?

23 A Yes.

24 Q So turning to DDX 6.83, did the Lovaza PDR identify a
25 problem with the Lovaza treatment that it describes?

12:11:56 1 A Yes. There was clearly a motivation to combine these.

12:12:00 2 So as we repeatedly stated, Lovaza elevates LDL
12:12:05 3 cholesterol, and they note in the Lovaza PDR that patients
12:12:08 4 should be monitored to ensure that the LDL level does not
12:12:12 5 increase excessively.

12:12:16 6 Mori showed that LDL cholesterol increased
12:12:18 7 significantly with DHA, but not with EPA.

12:12:25 8 Q So did Mori identify a solution to the problem described
12:12:29 9 in the Lovaza PDR?

12:12:30 10 A Yes, EPA.

12:12:31 11 Q And would a person of skill in the art have been
12:12:34 12 motivated to combine the Lovaza PDR in Mori?

12:12:39 13 A Yes.

12:12:39 14 Q Now, turning to DDX 6.84, would a person of skill in the
12:12:44 15 art have had a reasonable expectation of success in practicing
12:12:48 16 the method in claim 1 of the '929 patent?

12:12:51 17 A Yes. So claim 1 of the '929 patent was a method of
12:12:55 18 reducing triglycerides, and Mori specifically found an
12:12:59 19 18.4 percent reduction with EPA, almost identical to that
12:13:04 20 induced by DHA which was 20 percent.

12:13:07 21 Q Now, turning to DDX 6.85, do other prior art references
12:13:13 22 in your key prior art support your analysis of claim 1 of the
12:13:18 23 '929 patent?

12:13:19 24 A Yes. Two other publications, Hayashi '95, 1995, they
12:13:25 25 note that they were treating patients with EPA with a very

12:13:29 1 significant reduction in triglycerides of 41 percent.

12:13:33 2 And I'll note that this is a study which included at
12:13:36 3 least one, and probably several patients, that had
12:13:39 4 triglyceride levels of greater than 500.

12:13:42 5 Similarly, Kurabayashi 2000 showed a 27 percent
12:13:46 6 reduction in EPA that was highly significant, and that there
12:13:50 7 was no evidence for an increase in LDL cholesterol level in
12:13:54 8 that study with EPA treatment.

12:13:56 9 Q And in the Hayashi study, was there any significant
12:14:00 10 effect on LDL cholesterol?

12:14:03 11 A They state no statistically significant effect on LDL-C.

12:14:07 12 Q So, in your opinion, would the differences between the
12:14:10 13 prior art in claim 1 of the '929 patent have been obvious to a
12:14:14 14 person of skill in the art in March of 2008?

12:14:17 15 A Yes.

12:14:18 16 Q Let's turn to asserted claim 5 of the '929 patent
12:14:22 17 depicted on DDX 6.86.

12:14:26 18 What is the difference between this claim and claim
12:14:29 19 1 of the '929 patent that we just reviewed?

12:14:32 20 A It also requires that it be effective to reduce
12:14:35 21 apolipoprotein B, or apo B.

12:14:40 22 Q So turning to DDX 6.87, did the prior art disclose that
12:14:44 23 purified EPA reduces apo B?

12:14:48 24 A It did. Kurabayashi 2000 specifically states the
12:14:52 25 apolipoprotein B level in the EPA group was significantly

12:14:57 1 lower at week 48 compared with baseline, and they had these
12:15:01 2 results in a table.

12:15:02 3 We can see that in the control group there was a
12:15:05 4 nonsignificant 1.5 percent decrease in apo B, and a highly
12:15:10 5 significant 6.9 percent reduction in the EPA group with a P
12:15:15 6 value of less than .001; very significant.

12:15:19 7 Q So, in your opinion, would the differences between the
12:15:22 8 prior art in claim 5 of the '929 patent have been obvious to a
12:15:27 9 person of skill in the art in March 2008?

12:15:30 10 A Yes.

12:15:30 11 Q Which asserted claims did you analyze next?

12:15:35 12 A This would be the '728 Patent, claims 1 and 16.

12:15:41 13 Q Let's turn first to claim 1 of the '728 Patent, which is
12:15:45 14 depicted on DDX 6.89.

12:15:49 15 What is the first limitation you analyzed in this
12:15:52 16 claim?

12:15:52 17 A This would be,

12:15:53 18 "A method of reducing triglycerides in a
12:15:56 19 subject having a fasting baseline triglyceride level
12:15:58 20 of 500 milligrams per deciliter to about
12:16:02 21 1500 milligrams per deciliter."

12:16:03 22 Q And turning to DDX 6.90, with a snapshot from DX 1535,
12:16:10 23 page 3, was that limitation taught by the prior art?

12:16:13 24 A Yes. In the Lovaza PDR insert they specifically state
12:16:18 25 patients with very high triglyceride levels, greater than 500.

12:16:22 1 Q And turning to DDX 6.91, what is the next limitation in
12:16:27 2 claim 1 of the '728 Patent that you analyzed?

12:16:30 3 A It would be the oral administration of about 4 grams per
12:16:34 4 day of a pharmaceutical composition for a period of 12 weeks.

12:16:39 5 Q And turning to DDX 6.92, with a snapshot of DX 1535,
12:16:45 6 pages 2 and 3, was that limitation taught by the prior art?

12:16:49 7 A Yes. Again, in the Lovaza PDR 2007, they note oral
12:16:55 8 administration, daily dose of Lovaza, 4 grams per day, and the
12:17:01 9 study that supports that suggestion was of 16 weeks duration.

12:17:06 10 Q Turning to DDX 6.93, what is the next limitation in claim
12:17:12 11 1 of the '728 Patent that you analyzed?

12:17:14 12 A This would require a pharmaceutical composition of at
12:17:20 13 least 96 percent EPA, here expressed as the weight of all
12:17:25 14 fatty acids present.

12:17:28 15 Q I think you mentioned this earlier, but is this a
12:17:30 16 difference between the claim method of treatment and the
12:17:32 17 Lovaza PDR method?

12:17:32 18 A Yes. So this would be the improvement, the way they're
12:17:36 19 trying to address the problem of the LDL cholesterol increase.

12:17:41 20 Q And turning to DDX 6.94, with a snapshot of DX 1538,
12:17:47 21 page 2, what prior art do you rely on for the limitation
12:17:50 22 requiring 4 grams daily of 96 percent EPA?

12:17:56 23 A This would be the Mori publication 2000, where EPA was
12:18:01 24 administered at a dose of 4 point -- excuse me, 4 grams a day
12:18:04 25 daily and orally, and they note specifically that it was

1 a highly-purified preparation of EPA that was approximately
2 96 percent pure.

3 Q And turning to DDX 6.95, was there a motivation to
4 combine the Lovaza PDR and the Mori 2000 reference?

5 A Yes. With the Lovaza preparation, there could be a
6 dangerous increase in LDL cholesterol levels. There was a
7 desire to avoid that. Mori indicated that LDL cholesterol
8 levels significantly increased with DHA, but not with EPA.

9 So, in other words, EPA did not have the deleterious
10 effect on LDL cholesterol levels.

11 Q Now, turning to DDX 6.96, are there any other limitations
12 in claim 1 of the '728 Patent?

13 A It would be in a subject who is not receiving concomitant
14 lipid-altering therapy, and also to effect a reduction in
15 triglycerides without substantially increasing LDL-C.

16 Q And turning to DDX 6.97, with a snapshot of Mori again,
17 DX 1538, pages 2 and 3, would a person of skill in the art
18 have had a reasonable expectation of success in achieving that
19 claimed result?

20 A Yes. For example, in Mori, none of the subjects were
21 regularly taking any drugs known to lipid-alter metabolism.

22 And, furthermore, this study demonstrated a highly
23 significant decrease in triacylglycerols, another name for
24 triglycerides, of 18.4 percent with EPA.

25 And, again, they noted that in the DHA treated

group, but not in the EPA treated group, there was a significant increase in LDL cholesterol.

Q And turning to DDX 6.98, apart from Mori, does other prior art support your opinion on the reasonable expectation of success for claim 1 of the '728 Patent?

A Yes. The Hayashi '95 paper; the Kurabayashi 2000 paper.

Again, Hayashi demonstrated a very significant decrease in triglycerides, with no significant increase in LDL cholesterol, and there were certainly at least one patient in the study with a triglyceride of greater than 500.

Kurabayashi showed a 27 percent reduction in triglycerides in the EPA treated group, and in that particular study, there was no -- excuse me -- there was a decrease in LDL cholesterol levels in both of the groups in this particular study. Certainly, no increase in LDL cholesterol.

Q So turning to DDX 6.99, is there any other language in claim 1 of the '728 Patent that we have not yet discussed?

A Yes. So there was a specific requirement for a comparison to a second subject having a fasting baseline triglyceride level of 500 to 1500 milligrams per deciliter, who had not received the pharmaceutical composition and concomitant lipid-altering therapy.

Q Now, does the Court's construction, in your understanding of the term "compared to," require an actual comparison to a second subject?

1 A No. My understanding is that the claim construction was
2 interpreted in sort of a common sense manner where one might,
3 for example, be able to compare to the patients themselves
4 before they were on the therapy, so, in other words, if that
5 there was a reasonable expectation of success, rather than
6 having to compare the treatment with a placebo-controlled
7 group.

8 Q And, regardless, was Mori a placebo-controlled study that
9 showed the effects of EPA compared to patients who were not
10 taking it?

11 A Yes.

12 Q Would a person of skill in the art have expected purified
13 EPA to have the effects required by claim 1 of the '728
14 Patent, compared to patients who did not receive the drug?

15 A Yes.

16 Q So, in your opinion, would the differences between the
17 prior art in claim 1 of the '728 patent have been obvious to a
18 person of skill in the art in March 2008?

19 A Yes.

20 Q Let's turn to claim 16 of the '728 patent depicted here
21 on DDX 6.101.

22 What is the difference between this claim and claim
23 1 of the '728 patent that we just reviewed?

24 A This is a requirement for a highly-purified EPA
25 preparation where the other components of the preparation

1 comprised no more than about 0.6 percent by weight of all
2 fatty acids combined.

3 Q Was that level of purity taught in the prior art?

4 A Yes. That would be in the WO '900 patent application
5 where they state the composition comprises between 99.6 and
6 99.9 percent EPA.

7 99.6 percent purity means there's less than
8 0.4 percent contamination. That's clearly less than the
9 0.6 percent prescribed above.

10 Q And would a person of skill in the art have been
11 motivated to reach the highest purity that they could?

12 A Yes, of course.

13 And also I might note that the WO '900 patent also
14 specified specifically that there was less than 0.1 percent of
15 the DHA that had been previously demonstrated to increase LDL
16 cholesterol.

17 Q So, in your opinion, would the differences between the
18 prior art in claim 16 of the '728 patent have been obvious to
19 a person of skill in the art as of March 2008?

20 A Yes.

21 Q Which asserted claim did you analyze next?

22 A The '715 patent claims -- excuse me, claim 14.

23 Q So turning to DDX 6.103, does claim 14 of the '715 patent
24 depend from any other claims of the '715 patent?

25 A Yes, claim 13.

12:24:02 1 Q And what is the difference between claim 13 of the '715
12:24:06 2 patent and claim 1 of the '728 patent that you analyzed
12:24:10 3 earlier?

12:24:10 4 A To effect a statistically significant reduction in
12:24:13 5 triglycerides without effecting a statistically significant
12:24:17 6 increase in LDL cholesterol or apolipoprotein B.

12:24:22 7 Q Now, what is the difference between asserted claim 14 of
12:24:25 8 the '715 patent and claim 13 that it depends from?

12:24:32 9 A It states here,

12:24:37 10 "To effect a statistically significant
12:24:38 11 reduction in triglycerides in apo B without
12:24:43 12 effecting" -- excuse me here. I think I'm getting
12:24:45 13 this backwards here.

12:24:47 14 "To effect a statistically significant
12:24:49 15 reduction in triglycerides in apo B without effecting
12:24:53 16 a statistically significant increase in LDL-C in the
12:24:59 17 subject."

12:24:59 18 Q And turning to DDX 6.106, with snapshots DX 1534, pages 3
12:25:06 19 and 5, did the prior art teach the additional limitations of
12:25:10 20 claim 14 of the '715 patent?

12:25:12 21 A Yes. The Kurabayashi 2000, as I've cited several times
12:25:18 22 before, there was a significant decrease in the triglycerides.
12:25:21 23 There was no increase in LDL cholesterol, and there was a
12:25:25 24 significant reduction in apo B in the EPA-treated group of 7
12:25:31 25 percent.

12:25:31 1 Q So does Kurabayashi teach all of the effect limitations
12:25:35 2 in claim 14 of the '715 patent?

12:25:38 3 A Yes.

12:25:38 4 Q And would the differences between the prior art and claim
12:25:42 5 14 of the '715 patent have been obvious to a person of skill
12:25:45 6 in the art as of March 2008?

12:25:47 7 A In my opinion, yes.

12:25:51 8 Q Which asserted claims did analyze next?

12:25:53 9 A The '677 patent, claims 1 and 8.

12:25:58 10 Q Let's turn first to claim 1 of the '677 patent on
12:26:03 11 DDX 6.108.

12:26:05 12 What material difference, if any, is there between
12:26:08 13 this claim and claim 1 of the '728 patent that you analyzed in
12:26:13 14 depth earlier?

12:26:14 15 A There's no limitation on whether the patient is taking
12:26:17 16 concurrent lipid-alter therapy.

12:26:20 17 Q Does that difference affect your opinions on obviousness?

12:26:23 18 A No.

12:26:23 19 Q Do all of your opinions as to claim 1 of the '728 patent
12:26:28 20 apply equally to claim 1 of the '677 patent?

12:26:31 21 A Yes.

12:26:32 22 Q In your opinion, would the differences between the prior
12:26:35 23 art in claim 1 of the '677 patent have been obvious to a
12:26:40 24 person of skill in the art as of March 2008?

12:26:43 25 A Yes.

Q Let's turn, now, to claim 8 of the '677 patent depicted on DDX 6.109.

What is the difference between this claim and claim 1 of the '677 patent that we just reviewed?

A It would be to effect a reduction in apo B, and Kurabayashi 2000 demonstrated this. There was a 7 percent reduction in the EPA treated group -- I'll start over again.

The claim 8 of the '677 patent was to effect a reduction in apo B, and Kurabayashi 2000 demonstrated that effect.

Specifically, there was a 6.9 percent statistically significant reduction in apo B in the EPA group with no significant change in the control group.

Q So, in your opinion, would the differences between the prior art and claim 8 of the '677 patent have been obvious to a person of skill in the art as of March 2008?

A Yes.

Q Which asserted claim did you analyze next?

A The '652 patent, claim 1.

Q So let's turn to '652 patent, claim 1, depicted here on DDX 6.111.

What material difference, if any, is there between claim 1 of the '652 Patent, and claim 1 of the '728 patent that you analyzed earlier?

A There's no limitation on whether a patient is taking

12:28:31 1 concurrent lipid-altering therapy.

12:28:34 2 Q And, again, does that difference affect your obviousness
12:28:37 3 opinions?

12:28:37 4 A No.

12:28:38 5 Q So, in your opinion, would the differences between the
12:28:41 6 prior art and claim 1 of the '652 patent have been obvious to
12:28:46 7 a person of skill in the art in March of 2008?

12:28:49 8 A Yes.

12:28:53 9 Q Which asserted claims did you analyze next?

12:28:55 10 A The '560 patent, claims 4 and 7.

12:29:01 11 Q So let's turn first to claim 4 of the '560 patent, which
12:29:05 12 is on the screen on DDX 6.113.

12:29:09 13 Does this claim depend from any other claims of the
12:29:13 14 '560 patent?

12:29:14 15 A The method of claim 1.

12:29:17 16 Q And what material difference, if any, is there between
12:29:21 17 claim 1 of the '560 patent and claim 1 of the '728 patent that
12:29:26 18 you analyzed in depth earlier?

12:29:28 19 A There is no limitation on whether the patient is taking
12:29:32 20 concurrent lipid-altering therapy, and there's no limitation
12:29:35 21 on whether LDL-C increases.

12:29:38 22 Q Do those differences affect your obviousness opinions?

12:29:41 23 A No.

12:29:41 24 Q Do all your opinions as to claim 1 of the '728 patent
12:29:45 25 apply equally to claim 1 of the '560 patent?

12:29:49 1 A Yes.

12:29:50 2 Q So turning now to DDX 6.115, what is the difference
12:29:56 3 between claim 4 of the '560 patent and claim 1 that it depends
12:30:01 4 from?

12:30:01 5 A It effects a reduction in fasting triglycerides of at
12:30:05 6 least 10 percent without increasing LDL-C by more than 5
12:30:10 7 percent.

12:30:10 8 Q Were those limitations taught by the prior art that you
12:30:14 9 rely on?

12:30:15 10 A Mori, et al., in 2000 again, triglycerides decrease
12:30:19 11 significantly by 18 percent. In contrast, LDL cholesterol
12:30:24 12 increased significantly with DHA, but not with EPA.

12:30:28 13 Q So, in your opinion, would the differences between the
12:30:31 14 prior art in claim 4 of the '560 patent have been obvious to a
12:30:35 15 person of skill in the art as of March of 2008?

12:30:38 16 A Yes.

12:30:39 17 Q On the screen now is claim 17 of the '560 patent on
12:30:46 18 DDX 6.116.

12:30:47 19 Does claim 17 depend from any other claims of the
12:30:47 20 '560 patent?

12:30:52 21 A It depends on the method of claim 11.

12:30:55 22 Q And is there any material difference between claim 11 of
12:30:58 23 the '560 patent and claim 1 of the '560 patent --

12:31:03 24 A No.

12:31:03 25 Q -- that you analyzed earlier?

12:31:04 1 A No, there is not.

12:31:07 2 Q What is the difference between claim 17 of the '560
12:31:11 3 patent and claim 11 that it depends from?

12:31:13 4 A It effects a reduction in fasting triglycerides of at
12:31:16 5 least 20 percent without increasing LDL-C.

12:31:20 6 Q And you said at least 20 percent. Did you mean at least
12:31:23 7 about 20 percent?

12:31:25 8 A At least about 20 percent.

12:31:28 9 Q And, in your opinion, was that limitation taught by the
12:31:33 10 prior art?

12:31:33 11 A It was. In Mori, we showed at least about 18.4 percent
12:31:38 12 decrease in the triglyceride levels. It decreased
12:31:42 13 significantly by 18.4 percent.

12:31:44 14 Q And would a reduction in triglycerides of at least about
12:31:48 15 20 percent include a reduction of 18.4 percent in your
12:31:51 16 opinion?

12:31:51 17 A Yes. They also note -- I guess I should say -- never
12:31:58 18 mind.

12:32:00 19 Q Turning to DDX 6.118 --

12:32:03 20 A Yes.

12:32:03 21 Q -- did other prior art also teach the limitations in
12:32:07 22 claim 17 of the '560 patent?

12:32:09 23 A Yes. So there was a -- the claim of -- the method of
12:32:14 24 claim 11 and claim 17 effects a reduction in fasting
12:32:18 25 triglycerides of at least about 20 percent without increasing

12:32:22 1 LDL-C.

12:32:25 2 And in the Hayashi publication there was a
12:32:28 3 41 percent reduction in triglycerides with EPA, but no
12:32:32 4 significant effect on the LDL-C.

12:32:35 5 Q So, in your opinion, would the differences between the
12:32:37 6 prior art in claim 17 of the '560 patent have been obvious to
12:32:42 7 a person of skill in the art as of March 2008?

12:32:44 8 A Yes.

12:32:50 9 MR. REIG-PLESSIS: I'll just note, Your Honor,
12:32:51 10 this is another transition point.

12:32:54 11 THE COURT: Yes. So you just finished that
12:32:55 12 portion in about 30 minutes.

12:32:57 13 We'll take our lunch recess at this time then.
12:33:00 14 Thank you.

12:33:00 15 MR. REIG-PLESSIS: Thank you.

12:33:00 16 (The noon recess was taken.)

10:36:03 17 --o0o--
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10:36:03 1 RENO, NEVADA, WEDNESDAY, JANUARY 15, 2020, 1:23 P.M.

10:36:03 2 ---o0o---

01:23:22 3
01:23:22 4 THE COURT: Please be seated.

01:23:23 5 I'm sorry, Miss Clerk, are we ready?

01:23:33 6 THE CLERK: Yes, we are.

01:23:34 7 THE COURT: Mr. Reig, please resume.

01:23:35 8 MR. REIG-PLESSIS: Thank you, Your Honor.

01:23:36 9 DIRECT EXAMINATION RESUMED

01:23:36 10 BY MR. REIG-PLESSIS:

01:23:37 11 Q Good afternoon, Dr. Heinecke.

01:23:39 12 Now, did you consider potential counterarguments to
01:23:44 13 your opinions that Amarin has raised in this case?

01:23:49 14 A I did. I considered a number of potential
01:23:52 15 counterarguments, and the first one that I considered was
01:23:58 16 studies that found that DHA did not increase LDL cholesterol.

01:23:59 17 I would just like to mention the fact that simply
01:24:02 18 because DHA did not increase LDL cholesterol doesn't obviate
01:24:08 19 the potential advantage of using EPA alone to lower
01:24:08 20 triglycerides without elevating LDL cholesterol.

01:24:13 21 Q So turning to DDX 6.120, there's a snapshot on the screen
01:24:19 22 of DX 1933, pages 4 and 6, which is an exhibit that is on the
01:24:27 23 parties' admitted exhibit list.

01:24:29 24 Is this an article that Amarin has relied on as
01:24:33 25 evidence that DHA did not increase LDL-C?

01:24:36 1 A Yes, it is.

01:24:38 2 Q And could you identify this document.

01:24:40 3 A This would be Agren 1996 entitled "Fish Diet, Fish Oil
01:24:48 4 and DHA Rich Oil Lower Fasting and Postprandial Plasma Lipid
01:24:48 5 Levels."

01:24:57 6 And this study was a fairly complex design, four
01:25:00 7 different groups. It included a control group, a fish diet
01:25:05 8 group, a fish oil group, and a DHA oil group.

01:25:05 9 And I might mention that the DHA oil was not
01:25:11 10 particularly high purity. I believe, for example, that it had
01:25:15 11 20 percent myristic acid in the preparation so this was not a
01:25:15 12 highly-purified DHA preparation.

01:25:22 13 And the authors concluded that the only definite
01:25:25 14 conclusion which can be made on the basis of this study is
01:25:28 15 that DHA is effective in lowering fasting plasma triglyceride
01:25:34 16 levels.

01:25:34 17 Q Did the authors of Agren draw any definite conclusion
01:25:39 18 about whether DHA increases LDL-C?

01:25:42 19 A No, they did not.

01:25:43 20 Q Did Agren test purified EPA?

01:25:50 21 A No, they did not.

01:25:50 22 Q And was this study, the Agren 1996 study, before or after
01:25:54 23 the Mori 2000 study that directly compared the effects of EPA
01:25:59 24 and DHA on LDL-C?

01:26:04 25 A It was prior to that study.

01:26:06 1 Q So would a person of skill in the art in March of 2008
01:26:11 2 have relied on Agren 1996 to compare the effects of EPA and
01:26:14 3 DHA on LDL-C?

01:26:16 4 A Not in my opinion.

01:26:23 5 Q Turning now to DDX 6.121. There's snapshot of DDX 14 --
01:26:35 6 excuse me, DX 1949, which is on the parties' admitted exhibit
01:26:35 7 list.

01:26:37 8 Do you recognize this as another article that Amarin
01:26:38 9 has relied on for the effects of DHA on LDL-C?

01:26:42 10 A Yes. This would be the Conquer publication 1996 where
01:26:47 11 they investigated the effect of dietary supplementation with
01:26:53 12 an algae source of DHA devoid of any EPA.

01:26:56 13 Q And, again, did Conquer test purified EPA or compare it
01:27:00 14 to DHA?

01:27:01 15 A No, they simply stated that they were using a preparation
01:27:03 16 of DHA that was devoid of EPA.

01:27:06 17 Q And was this study before or after the Mori 2000 study
01:27:11 18 that directly compared EPA and DHA's effects on LDL-C?

01:27:16 19 A It was prior to that study.

01:27:18 20 Q So would a person of skill in the art in March of 2008
01:27:21 21 have relied on Conquer to compare EPA and DHA?

01:27:26 22 A Not in my opinion.

01:27:28 23 Q Turning now to DDX 6.122, there's a snapshot of DX 1961
01:27:38 24 with a call-out from page 3. This document is also on the
01:27:43 25 admitted exhibits list.

01:27:45 1 Do you recognize this as another article that Amarin
01:27:48 2 has relied on as evidence that DHA did not increase LDL-C?

01:27:53 3 A Yes. This would be Rambjør 1996 entitled "EPA is
01:27:59 4 Primarily Responsible For Hypotriglyceridemic Effect of Fish
01:28:04 5 Oil in Humans."

01:28:05 6 Q And what finding in particular has Amarin relied on from
01:28:09 7 Rambjør?

01:28:10 8 A Well, first I note that the title emphasizes that it's
01:28:13 9 EPA that's primarily responsible for the hypotriglyceridemic
01:28:20 10 effect of fish oil.

01:28:20 11 But the deleterious thing that they reported was an
01:28:22 12 increase in LDL cholesterol levels, and, in contrast, they did
01:28:26 13 not see any evidence that DHA supplementation affected LDL
01:28:30 14 levels, and so this would be in contrast to the studies that I
01:28:33 15 reported earlier.

01:28:35 16 Q Did Rambjør show that DHA affected triglyceride levels?

01:28:40 17 A It states specifically there that it did not affect
01:28:44 18 triglyceride levels.

01:28:45 19 Q Is that consistent with the other literature on DHA?

01:28:49 20 A No.

01:28:50 21 Q Does the fact that some studies showed an increase in
01:28:56 22 LDL-C and some showed a decrease in LDL-C consistent with the
01:29:02 23 conclusion that EPA is actually LDL neutral?

01:29:02 24 A In my opinion, yes, that would indicate, for example, if
01:29:07 25 there was one-third of the studies showing an increase,

01:29:09 1 one-third of the study showing a decrease, and one third of
01:29:12 2 the study showing no effect, that would be very strong
01:29:15 3 evidence that there was no overall effect of the intervention.

01:29:18 4 Q So turning to DDX 6.123, there's no snapshot from
01:29:24 5 DX 1961, pages 4 and 6.

01:29:28 6 Did the authors of the Rambjør 1996 study express
01:29:32 7 any doubts about their findings?

01:29:36 8 A Well, I'll state the conclusions they made first and then
01:29:39 9 offer some reasons why they state that.

01:29:41 10 They explicitly say that further studies are needed
01:29:45 11 to clearly define the individual effects of the EPA and DHA on
01:29:49 12 human lipid metabolism, and I believe this paper has a number
01:29:54 13 of serious defects, but one of them was the overall study
01:29:58 14 design.

01:29:58 15 So you'll notice, as highlighted in the first
01:30:01 16 sentence at the top the paragraph, the DHA group was
01:30:05 17 relatively small. There were only nine subjects in that
01:30:09 18 group, versus 25 in the EPA group and 35 in the control fish
01:30:15 19 oil group.

01:30:16 20 So thus it's severely underpowered, and, in fact,
01:30:20 21 it's very unusual to try and compare studies that have very
01:30:24 22 large numbers of subjects in one group and a very small number
01:30:27 23 of subjects in another group. So I think that's a study
01:30:30 24 design flaw.

01:30:30 25 And they themselves conclude we cannot be sure that

1 it would have had an effect in a larger group.

2 And they also note consistent with this observation
3 the percent change in LDL-C was identical for both EPA and
4 DHA, and I think this again points to the issue of random
5 variation with small numbers of subjects where one might by
6 chance observe an increase or a decrease that was simply that
7 chance.

8 So -- and they, themselves, conclude the smaller
9 number of subjects in the later group prevented the difference
10 from being significant.

11 So, in other words, both groups had an increase in
12 LDL-C, but because of the small number in the DHA group, it
13 was not significantly significant.

14 Q Now, turning to DDX 6.124, you mention the need for
15 further studies expressed in Rambjør 1996. Was Mori 2000 a
16 further study after Rambjør that clarified the different
17 effects of EPA and DHA?

18 A It was. It showed that LDL cholesterol significantly
19 increased in the DHA group but not in the EPA group.

20 I'll note that this study had about 20 to 25
21 subjects per group so obviously it was better powered to
22 answer the question.

23 Moreover, Maki in 2005 note that most previous
24 studies of DHA supplementation have shown increases in LDL
25 concentration, and note again how they're very careful to cite

1 a range of studies but that the range is minus three percent
2 to plus 16 percent with a median of eight percent, and this
3 would be very consistent with the idea that there's a
4 significant increase overall when one considers all of the
5 available evidence.

6 Q Now, turning to DDX 6.125, there's a snapshot of DX 1538
7 from pages 5 and 9.

8 Did the Mori 2000 reference itself address Rambjør?

9 A They did. They specifically mentioned it.

10 And they pointed out another limitation of this
11 study so -- I didn't go into the study design, but this is a
12 complicated crossover study design where they would use one
13 intervention, and then use a washout period, and then have a
14 second intervention.

15 And they noted that the washout period between the
16 two interventions was very short, only two weeks, and that
17 there could have been confounding effects of the previous
18 treatment on the subsequent treatment.

19 And they specifically mention this as a limitation,
20 along with the short duration of treatment in a small number
21 of subjects of the Rambjør paper.

22 Q And do you agree with Mori's assessment of the Rambjør
23 paper?

24 A I think that's a very reasonable assessment.

25 Q In your opinion, would a person of skill in the art as of

01:33:18 1 March of 2008 have relied on the Rambjør study from 1996?

01:33:23 2 A No.

01:33:27 3 Q So now on the screen is DDX 6.126 it's a snapshot from
01:33:33 4 DX 1605.

01:33:36 5 Is this another reference that Amarin has relied on
01:33:40 6 in this case?

01:33:40 7 A Yes, von Schacky 2006 is a reference that they relied
01:33:44 8 upon.

01:33:47 9 So let me state this is a review as mentioned in the
01:33:52 10 article. There is no primary data in this paper. So this is
01:33:55 11 summary of this author's interpretation of what the literature
01:33:59 12 shows.

01:34:02 13 MR. REIG-PLESSIS: Your Honor, we would move in
01:34:04 14 DX 1605 into evidence.

01:34:07 15 MR. SIPES: No objection.

01:34:07 16 THE COURT: 1605 is admitted.

01:34:07 17 (Defendants' Exhibit 1605 received in
01:34:11 evidence.)

01:34:11 18 BY MR. REIG-PLESSIS:

01:34:13 19 Q So did von Schacky provide any new clinical data beyond
01:34:16 20 what was already reported in the literature?

01:34:18 21 A Well, as stated in the title, it's a review. There's no
01:34:21 22 primary data in this publication.

01:34:26 23 Q Now, turning to DDX 6.127, do you understand that Amarin
01:34:29 24 has relied on table 1 of von Schacky as evidence that EPA and
01:34:35 25 DHA were believed to have the same effect on LDL-C?

01:34:40 1 A Yes.

01:34:40 2 Q Do you agree with Amarin's view?

01:34:44 3 A Well, as the authors themselves state -- this is kind of
01:34:49 4 a curious figure actually.

01:34:50 5 So we have these arrows, and, of course, I would
01:34:53 6 agree that an arrow pointing up or an arrow pointing down or
01:34:57 7 sideways, would tend to point towards an increase or no change
01:35:01 8 or a decrease.

01:35:02 9 But as they, themselves, note it's semiquantitative.
01:35:06 10 And really the significance of these arrows is totally
01:35:10 11 unclear. There's nothing attached to one arrow, two arrows,
01:35:13 12 is it one percent, is it ten percent?

01:35:16 13 I find -- I find this a very difficult figure to
01:35:23 14 interpret.

01:35:23 15 And I'll point out another issue here. They cite
01:28:35 16 Rambjør in support of their interpretations, and then they
01:35:29 17 also cite Mori which did not provide conclusions that were
01:35:34 18 much stronger than Rambjør that would contradict their
01:35:37 19 assessments on the LDL cholesterol changes.

01:35:41 20 So I think this is a very difficult table to
01:35:45 21 interpret, and I also think it suggests that the author is not
01:35:49 22 properly interpreting the available literature.

01:35:52 23 Q In your opinion, did it make sense for von Schacky to
01:35:56 24 cite Rambjør as a relative study in 2006?

01:36:00 25 A If I were the author of the paper, I wouldn't have done

01:36:04 1 that.

01:36:04 2 Q And does von Schacky change your opinion on how a person
01:36:07 3 of skill in the art would have interpreted the actual clinical
01:36:10 4 data in Mori?

01:36:11 5 A No.

01:36:12 6 Q Now, since von Schacky was published, has Amarin itself
01:36:17 7 relied on the Mori 2000 paper?

01:36:18 8 A Yes, it has.

01:36:21 9 Q So turning to DDX 6.128 on the screen is DX 1741, pages 7
01:36:30 10 and 9.

01:36:31 11 Could you identify this document, please.

01:36:33 12 A Yes. This would be the Bays 2011 paper that we've heard
01:36:40 13 so much about, the Amarin MARINE study, which was a very high
01:36:43 14 quality study of the impact of their compound, the
01:36:46 15 highly-purified EPA on triglyceride and LDL cholesterol levels
01:36:51 16 in patients with elevated triglycerides, the MARINE study.

01:36:55 17 MR. REIG-PLESSIS: Defendants move in the
01:36:57 18 admission of DX 1741.

01:36:59 19 MR. SIPES: No objection, Your Honor.

01:37:01 20 THE COURT: 1741 admitted.

01:37:01 21 (Defendants' Exhibit 1741 received in
01:37:03 evidence.)

01:37:03 22 BY MR. REIG-PLESSIS:

01:37:04 23 Q Did Amarin cite Mori 2000 in the Bays MARINE publication?

01:37:08 24 A They did. They state in several small previous studies,
01:37:12 25 and note that the references are circled there, 14 through 16,

01:37:15 1 and one of those references is Mori, reference 15.

01:37:21 2 Q And for what proposition did Amarin cite Mori in the Bays
01:37:27 3 MARINE publication?

01:37:27 4 A They're specifically discussing the influences of DHA
01:37:33 5 treatment and EPA treatment on LDL cholesterol levels. So, in
01:37:38 6 other words, they're summarizing what their interpretation of
01:37:40 7 the previous literature is.

01:37:42 8 And they concur that although DHA treatment
01:37:45 9 generally increased LDL cholesterol levels, EPA therapy did
01:37:50 10 not. This is the MARINE study from Amarin.

01:37:53 11 Q Now, did Amarin cite von Schacky or would not in the Bays
01:38:00 12 MARINE publication?

01:38:01 13 A No, they did not.

01:38:02 14 Q Turning to DDX 6.129, with snapshots of pages 7 and 9
01:38:09 15 from the same exhibit, DX 1741.

01:38:12 16 Did Amarin also cite other prior art that you rely
01:38:16 17 on?

01:38:16 18 A Yes. They specifically commented on LDL cholesterol
01:38:21 19 levels, and what they mentioned was that smaller trials of
01:38:24 20 patients with normal to moderately elevated triglyceride
01:38:28 21 levels suggested that purified EPA might reduce triglyceride
01:38:31 22 levels without increasing LDL cholesterol levels, and they
01:38:35 23 specifically cite the Kurabayashi reference that I've cited
01:38:39 24 repeatedly.

01:38:39 25 Q And based on smaller trials that suggested that purified

01:38:44 1 EPA might reduce triglyceride levels without increasing LDL in
01:38:48 2 patients with normal to moderately elevated triglyceride
01:38:52 3 levels, was there a reasonable expectation that that same
01:38:56 4 result would occur in patients with very high triglycerides?

01:39:00 5 A Yes, in my opinion.

01:39:03 6 Q And why is that?

01:39:04 7 A Well, typically, if one observes effect on a value at a
01:39:04 8 lower level, one anticipates seeing a similar effect at higher
01:39:04 9 levels of that value.

01:39:12 10 And, again, I would use the example of blood
01:39:15 11 pressure medications where blood pressure medications lower
01:39:18 12 blood pressure in people with low blood -- you know, moderate
01:39:21 13 elevations of blood pressure and high levels of blood
01:39:25 14 pressure -- I know.

01:39:26 15 THE COURT: Slow down.

01:39:30 16 THE WITNESS: I know. I better cut down on the
01:39:32 17 coffee here.

01:39:33 18 Let me start over again, excuse me.

01:39:34 19 So, in general, with most medications, one sees
01:39:38 20 a similar effect at lower elevations and higher elevations,
01:39:43 21 and, of course, medicine being medicine, nothing is universal.
01:39:47 22 But in general, that is a consistent theme.

01:39:50 23 So it would be very reasonable to expect that an
01:39:53 24 intervention that lowers triglyceride levels, for example, at
01:39:57 25 lower triglyceride levels would also lower them at higher

1 triglyceride levels.

2 Now, lipoproteins are complicated, and things
3 are not always that simple, but in general that's what one
4 would anticipate.

5 BY MR. REIG-PLESSIS:

6 Q Is Amarin's reliance on the Mori and Kurabayashi papers
7 in the Amarin MARINE publication consistent with your own
8 opinions about those references?

9 A Yes, it is.

10 Q Did you also consider the argument that DHA may have
11 certain advantages over EPA?

12 A Yes, I did.

13 Q So turning to DDX 6.131, there's a snapshot of DX 1538,
14 the Mori study we reviewed earlier, pages 3 and 5.

15 Do you understand Amarin has argued that Mori
16 suggested that DHA was more effective than EPA for reducing
17 triglycerides?

18 A Yes, I do. And I'll just point out that the Mori study
19 did show a significant decrease in triglycerides by EPA, and
20 that it reduced triglycerides to a similar extent as DHA. So
21 EPA and DHA are approximately equally effective at reducing
22 triglycerides.

23 Q And did the authors of Mori agree with your
24 interpretation of the data?

25 A Yes, and no. They certainly acknowledge that they both

01:41:21 1 reduced triglycerides to the same extent but they also had
01:41:25 2 other conclusions.

01:41:27 3 Q So turning to DDX 6.132, there's another snapshot from
01:41:33 4 Mori DX 1538, page 8.

01:41:37 5 Has Amarin argued that Mori disclosed any other
01:41:40 6 advantages of DHA?

01:41:42 7 A They have, and I want to emphasize this is the author's
01:41:46 8 interpretation of the data here. Okay?

01:41:49 9 So -- and I might mention one other thing. One
01:41:52 10 generally doesn't get your publications into a good journal by
01:41:56 11 emphasizing the negative findings in your work, and so there's
01:42:01 12 always a natural tendency for writers of scientific papers to
01:42:05 13 try and point out the most positive aspects of their work.

01:42:09 14 So what Mori here is doing is highlighted what they
01:42:13 15 thought was interesting or positive about DHA and they
01:42:17 16 specifically mention increased HDL cholesterol, a change in
01:42:23 17 LDL particle size which increased, and increased fasting blood
01:42:28 18 glucose concentrations that were induced by EPA but not DHA
01:42:33 19 which would relate potentially to insulin sensitivity and the
01:42:35 20 risk of diabetes.

01:42:37 21 Q And were these parameters seen by some people as
01:42:42 22 potential advantages of certain therapies?

01:42:44 23 A Yes. There's always been intense interest in biomarkers
01:42:48 24 for cardiovascular risk, and many, many investigators focus on
01:42:52 25 these.

1 The number of these risk factors it's actually
2 turned out to be clinically significant is rather small. I
3 might cite my own area of research which is HDL cholesterol
4 which everyone thought good cholesterol.

5 But then and now there's no randomized clinical
6 trial evidence that elevating HDL cholesterol is beneficial in
7 reducing cardiovascular risk.

8 Q So, in your opinion, would a person of skill in the art
9 in March of 2008 have focused on HDL cholesterol, LDL particle
10 size, or fasting glucose as being more important than LDL
11 cholesterol levels?

12 A Not in my opinion, and certainly not if they based it on
13 randomized clinical trial data.

14 Q So turning to DDX 6.133, this demonstrative has snapshots
15 from DX 1876, the ATP III publication we reviewed earlier from
16 pages 27, 39 through 40 and 42.

17 Did ATP III address the factors that Amarin relies
18 on as advantages of DHA over EPA?

19 A It did. And let me point out that ATP III was the
20 guidelines that said that the major emphasis for treatment
21 should be LDL cholesterol.

22 The advantage potentially of using EPA which avoids
23 an increase in LDL cholesterol, it was identified as the major
24 determinant for cardiovascular risk to focus on.

25 They also did address HDL cholesterol, LDL particle

01:44:31 1 size, and fasting glucose.

01:44:35 2 As noted for HDL cholesterol, and it has turned out
01:44:39 3 to be depressingly true, raising of HDL cholesterol levels
01:44:43 4 will not reduce CHD risk as much as might be predicted from
01:44:47 5 prospective epidemiological studies, and this illustrates a
01:44:51 6 major limitation of epidemiology which is very few of the
01:44:54 7 observations that are made in epidemiology are confirmed in
01:44:58 8 randomized clinical trials.

01:45:01 9 And I might mention vitamin D, for example, we've
01:45:04 10 heard so much about for the last decade. A whole series of
01:45:11 11 randomized chemical trials are coming out now -- that's
01:45:11 12 hindsight, excuse me. I withdraw that statement.

01:45:15 13 Excuse me. Strike that. Is that right thing to
01:45:17 14 say.

01:45:17 15 THE COURT: I don't know if you get to strike
01:45:20 16 testimony.

01:45:21 17 THE WITNESS: That's hindsight. I will admit
01:45:21 18 that that's hindsight.

01:45:24 19 LDL particle size, ATP III does not recommend
01:45:28 20 measurement of small LDL particles in routine practice, and
01:45:33 21 there certainly has been intense interest in small LDL
01:45:36 22 particles, very abundant literature on this.

01:45:40 23 I might mention that small LDL is about
01:45:45 24 .2 nanometers, smaller than regular LDL which is
01:45:51 25 22 nanometers, so a one percent difference. And, in my

01:45:55 1 opinion, most clinicians now and then would not regard that as
01:46:00 2 being significantly different in terms of cardiovascular risk.

01:46:04 3 At the time of ATP III, fasting blood glucoses
01:46:10 4 were not strongly considered to be cardiovascular risk, and it
01:46:14 5 says at the bottom there,

01:46:15 6 "Neither does it count as a risk factor to
01:46:18 7 modify LDL cholesterol goal."

01:46:21 8 So I think, again, these are possible benefits,
01:46:23 9 but I believe that most clinicians would have focused on the
01:46:27 10 LDL cholesterol changes.

01:46:29 11 BY MR. REIG-PLESSIS:

01:46:29 12 Q So turning to DDX 6.134, based on the guidance in
01:46:36 13 ATP III, what actual data in Mori 2000 would a person of skill
01:46:40 14 in the art in March of 2008 have been focused on?

01:46:43 15 A As emphasized by APT III, I think that most clinicians
01:46:48 16 would have focused on LDL cholesterol which increased
01:46:51 17 significantly with DHA but not with EPA.

01:46:54 18 Q Turning to DDX 6.135, which has another snapshot from the
01:47:01 19 von Schacky reference we reviewed earlier, DX 1605, page 9,
01:47:07 20 has Amarin cited other advantages that DHA might have over
01:47:12 21 EPA?

01:47:12 22 A It has. I've already referred to the HDL cholesterol.
01:47:18 23 There's also been interest in platelet aggregation. That
01:47:21 24 relates to the ability for platelets to form clots which
01:47:24 25 triggers a heart attack.

1 There's been interest in heart rate modulation, and
2 something else called endothelial function which has to do
3 with how well your blood vessels relax.

4 All of these have been proposed to be very
5 significant cardiovascular risk factors.

6 Again, in my opinion there's no randomized clinical
7 trial evidence that any of these are clinically significant.

8 Q Would a person of skill in the art in March of 2008 have
9 viewed these parameters as taking precedence over LDL-C
10 levels?

11 A Not in my opinion, no.

12 Q Now, even assuming that the prior art taught a preference
13 for DHA, would that have made the use of purified EPA any less
14 obvious in your opinion?

15 A In my opinion, no.

16 Q Is there a legal standard you've been informed about that
17 supports your opinion?

18 A Yes, my understanding is a prior art reference does not
19 teach a way if it merely expresses a general preference for an
20 alternative invention.

21 So clearly these authors are offering a preference
22 for an alternative approach, but that does not negate the
23 advantage of not raising LDL cholesterol.

24 Q Is it possible that both purified EPA and purified DHA
25 were obvious?

01:48:47 1 A Well, yes. It's -- yes.

01:48:54 2 Q Now, do you understand that Amarin has criticized your
01:48:57 3 reliance on studies in patients with triglycerides below 500?

01:49:03 4 A I do.

01:49:03 5 Q Is there any material difference between, for example,
01:49:06 6 triglycerides of 400 and 500?

01:49:11 7 A Well, as we've already heard, one the hallmarks of it is
01:49:16 8 that they vary widely over time, and so a patient could very
01:49:21 9 easily have a triglyceride value of 400 or 450 one day and
01:49:26 10 have a triglyceride value of 550 or 600 the next day. And in
01:49:31 11 fact we see the same thing with LDL cholesterol which varies
01:49:36 12 much less.

01:49:36 13 If you follow the same patient over time for LDL
01:49:39 14 cholesterol, it can vary over a 20 percent range. So this is
01:49:42 15 why it's very important to have multiple lipid measurements
01:49:48 16 before making treatment decisions.

01:49:49 17 And, moreover, I do not believe that there's kind of
01:49:49 18 magical mechanistic difference between 500 milligrams per
01:49:57 19 deciliter and 600 milligrams per deciliter and 400 milligrams
01:49:58 20 per deciliter.

01:49:59 21 The concern with pancreatitis is when one actually
01:50:02 22 gets up above the 1000-milligram per deciliter, and this was
01:50:06 23 something that was not well understood back in 2008. We knew
01:50:11 24 that somewhere above 500 milligrams per deciliter the system
01:50:15 25 for clearing triglycerides jams up. But no one knew what that

01:50:19 1 level was, but, we knew it was above 500 milligrams per
01:50:25 2 deciliter.

01:50:25 3 So the idea here was to be well below the level
01:50:29 4 where one worries about the triglyceride clearance system
01:50:32 5 jamming up, and then, under those circumstances, the
01:50:34 6 triglycerides would go sky high.

01:50:37 7 Let me just use an analogy here. The idea would be,
01:50:40 8 for example, if you had a tub with a hole in it and the water
01:50:43 9 would be pouring out of the bottom. That would be the
01:50:46 10 clearance of triglycerides.

01:50:48 11 If you jam up that plug, you're going to fill up the
01:50:51 12 tub very rapidly and greatly increase the level of the water
01:50:55 13 in the tub. That happens somewhere up above 500 milligrams
01:50:59 14 per deciliter, and we still don't know exactly where that is,
01:51:03 15 but it's probably in the 1000-milligram per deciliter range.

01:51:07 16 Q In general, do the qualitative effects of medications
01:51:11 17 depend on baseline triglycerides that patients have?

01:51:15 18 A Qualitatively, they tend to be the same.

01:51:20 19 Q Now, turning to DDX 6.138, there is a snapshot on the
01:51:26 20 screen of DX 1500, the '728 patent which is already in
01:51:31 21 evidence, from page 14.

01:51:35 22 As far as you can tell from reviewing the patents,
01:51:38 23 did the inventors of the asserted patents in this case
01:51:41 24 themselves place any significance on the 500-milligram per
01:51:45 25 deciliter threshold?

01:51:47 1 A I can't comment on whether they placed significance on
01:51:50 2 it, but what I can comment on is the facts which are that they
01:51:55 3 cite a level of at least or about 300 milligrams per
01:52:00 4 deciliter, at least or about 400 milligrams per deciliter, at
01:52:04 5 least or about 500 milligrams per deciliter, at least or about
01:52:08 6 600 milligrams per deciliter, at least or about 700 milligrams
01:52:13 7 per deciliter.

01:52:13 8 Do I need to keep going? They go all the way up to
01:52:18 9 1500 milligrams per deciliter there.

01:52:20 10 So I don't know what they were thinking, but this
01:52:24 11 doesn't accord very well with the idea that 500 milligrams per
01:52:28 12 deciliter is a critical threshold.

01:52:31 13 Q Now, turning to DDX 6.139, there is a snapshot from
01:52:36 14 DX 1526, page 28, the executive summary of ATP III that we
01:52:43 15 reviewed earlier.

01:52:44 16 Is it surprising that most references in the prior
01:52:48 17 art did not focus on patients with triglycerides above 500?

01:52:52 18 A In my opinion, no. I mean, as I think we've already
01:52:56 19 heard, triglyceride elevations in this range are fairly rare,
01:53:01 20 greater than 500 milligrams per deciliter, so this makes it
01:53:05 21 very difficult to carry out clinical studies with large
01:53:10 22 numbers of subjects.

01:53:11 23 Q And turning to DDX 6.140, regardless, did you rely on
01:53:19 24 prior art that disclosed the administration of purified EPA to
01:53:19 25 patients with triglycerides above 500?

01:53:22 1 A Yes. So I just wanted to emphasize, and I've already
01:53:26 2 shown this slide several times, the point of these five slides
01:53:33 3 is to indicate that there have been patients treated with EPA
01:53:38 4 that had triglyceride levels that are higher than 500, and
01:53:42 5 I've cited this repeatedly so I won't go through this again.

01:53:46 6 I do want to make one point here. I'm not arguing
01:53:50 7 that we know that EPA lowers LD -- lowers triglycerides
01:53:55 8 without lowering -- let me start over again.

01:53:59 9 I'm not arguing here that we know what the impact is
01:54:03 10 of EPA on LDL cholesterol levels above 500 milligrams per
01:54:08 11 deciliter.

01:54:09 12 We can't conclude that from these studies because,
01:54:12 13 first of all, we don't really know what the values are of the
01:54:15 14 individual patients in these studies, and, second of all,
01:54:18 15 there's a limitation of the method used to quantify LDL
01:54:22 16 cholesterol.

01:54:23 17 So LDL cholesterol -- let me take a step back. So
01:54:28 18 cholesterol is carried in both VLDL and LDL particles, and
01:54:33 19 what is done in most clinical studies for cost-effectiveness
01:54:36 20 is to measure the total cholesterol and the HDL cholesterol
01:54:41 21 and then to estimate the LDL cholesterol using an equation
01:54:45 22 called the Friedewald equation.

01:54:47 23 And what the equation does is use the triglycerides
01:54:50 24 to estimate the VLDL contribution to the LDL cholesterol, and
01:54:55 25 that equation is not accurate for triglycerides above

01:54:59 1 400 milligrams per deciliter.

01:55:01 2 And so I don't think there's any evidence in the
01:55:04 3 prior literature about what the impact of EPA would be on LDL
01:55:09 4 cholesterol in patients with triglycerides above
01:55:13 5 500 milligrams per deciliter.

01:55:15 6 But what I do think there is strong evidence of is
01:55:17 7 that EPA will lower triglycerides in these subjects.

01:55:22 8 Q Now, based on these studies, was there a reasonable
01:55:30 9 expectation that EPA would not have LDL-C effects in patients
01:55:35 10 above 500 in terms of triglycerides?

01:55:37 11 A In my opinion, yes.

01:55:39 12 Q And why is that?

01:55:41 13 A Because there were multiple studies showing that it would
01:55:43 14 lower triglycerides, and it would do so either without
01:55:48 15 elevating LDL cholesterol, in some cases with lowering LDL
01:55:53 16 cholesterol, and I'd also mention that in some cases there's
01:55:56 17 been a reduction in apo B that was significant, and that's
01:56:00 18 also another marker for LDL.

01:56:02 19 Q And would a person of skill in the art have expected a
01:56:05 20 different result in patients above 500?

01:56:08 21 A In my opinion, no.

01:56:09 22 Q Now, do you understand Amarin is arguing that
01:56:13 23 triglyceride-lowering drugs have different effects on LDL-C
01:56:17 24 depending on whether a patient's triglycerides are above or
01:56:20 25 below 500?

01:56:21 1 A Yes, I do.

01:56:22 2 Q And do you understand Amarin has relied on clinical data
01:56:26 3 with fibrates --

01:56:27 4 A Yes.

01:56:28 5 Q -- to support its theory?

01:56:30 6 What are fibrates?

01:56:32 7 A Fibrates are a class of drugs that lower triglycerides by
01:56:37 8 an unknown mechanism. They're typically, in the preEPA days,
01:56:43 9 were oftentimes the first or second line of choice for
01:56:46 10 lowering triglycerides in patients because they're very
01:56:49 11 effective at lowering triglycerides.

01:56:51 12 Q Are fibrates omega-3 fatty acids?

01:56:56 13 A They're completely unrelated. There's no structural
01:56:59 14 similarities between fibrates and omega-3 fatty acids, and, in
01:57:04 15 my opinion, there's no evidence that they share similar
01:57:06 16 mechanisms of action.

01:57:08 17 In fact, I don't believe that we know how EPA is
01:57:12 18 working, although I have a few ideas on that, and there's some
01:57:16 19 evidence from animal studies that fibric acid derivatives work
01:57:19 20 through PPAR receptors -- I won't go into the basic science.

01:57:22 21 That data is based almost exclusively on animal
01:57:26 22 data, not human data, and, in my opinion, we don't really know
01:57:30 23 how fibric acids are working in humans either.

01:57:34 24 Q Is fibric acids another word for fibrates?

01:57:37 25 A Yes, fibrates, or Fenofibrate, clofibrate, there's a

01:57:38 1 whole family of the fibric acid derivatives.

01:57:44 2 Q Are fibrates found in fish oil?

01:57:46 3 A No.

01:57:48 4 Q And would a person of skill in the art in March of 2008
01:57:52 5 have assumed that EPA had the same mechanism of action as
01:57:57 6 fibrates?

01:57:57 7 A Not in my opinion.

01:58:00 8 Q Now, did Amarin raise its argument about fibrates during
01:58:03 9 the prosecution of these patents?

01:58:05 10 A Yes, it did.

01:58:06 11 Q So turning to DDX 6.141, there's a snapshot of DX 1587,
01:58:16 12 page 19.

01:58:17 13 Do you recognize DX 1587 as a rejection by the
01:58:22 14 examiner dated August 18th, 2011?

01:58:26 15 A Yes, I do.

01:58:29 16 And the examiner specifically states here,

01:58:33 17 "Triplex (fenofibric acid)," it's a fibric

01:58:37 18 acid, "is structurally and biologically very

01:58:41 19 different from EPA-E (an omega-3 fatty acid).

01:58:46 20 Triplex is structurally a fibrate," and this family

01:58:50 21 "are known to reduce cholesterol by interacting with

01:58:50 22 the PPAR-alpha receptor."

01:58:56 23 I would say that we know that's one potential
01:58:59 24 mechanism in mice based on studies using mice that are
01:59:03 25 deficient in the PPAR-alpha receptor. Whether those studies

are relevant to humans I think remains an open question.

On the other hand, EPA is an omega-3 fatty acid to lower triglycerides, although the mechanism is not known, and the examiner concludes,

"So one cannot extrapolate the results observed with a fibrate to omega-3 fatty acids like EPA-E," and I would concur with that.

MR. REIG-PLESSIS: And, Your Honor, we would move the admission of DX 1587.

MR. SIPES: No objection.

THE COURT: 1587 is admitted.

(Defendants' Exhibit 1587 received in evidence.)

BY MR. REIG-PLESSIS:

Q Now, turning to DDX 6.142, there's a snapshot of DX 1591, the Notice of Allowance we reviewed earlier at page 9.

Earlier you testified that the examiner ultimately made a mistake in the Notice of Allowance. Despite that mistake, did the examiner agree with you that the differences between the claims and the prior art were obvious?

A Initially they did, and so, as stated here, based on these references, it was concluded that it would be obvious to treat patients having triglycerides above 500 milligrams per deciliter with 96 percent pure EPA.

Q And was that statement in the notice of allowance for these patents?

02:00:32 1 A Yes, the Notice of Allowance September 6, 2012.

02:00:36 2 Q Now, turning to DDX 6.143 with a snapshot of the same
02:00:45 3 exhibit, DX 1587, from pages 10 to 12.

02:00:49 4 If the examiner found that the differences between
02:00:52 5 the prior art and the claims were obvious, why did the
02:00:55 6 examiner allow the claims to issue?

02:00:57 7 A There were two reasons offered for the rejection of
02:01:02 8 obviousness. The first was unexpected results.

02:01:06 9 And specifically they referred to a significant
02:01:09 10 reduction of apo-B levels, here quoted as 8.5 percent from the
02:01:16 11 MARINE study.

02:01:17 12 And then they secondly noted a long felt, unmet
02:01:21 13 need, and this would refer to "not only reduces the levels of
02:01:26 14 triglycerides, but also does not increase LDL-C."

02:01:30 15 Q And do you understand that unexpected results and long
02:01:34 16 felt unmet need are secondary considerations in the
02:01:38 17 obviousness analysis?

02:01:39 18 A Yes, I do.

02:01:40 19 Q Did you analyze the secondary considerations that the
02:01:46 20 examiner relied on to allow the claims?

02:01:48 21 A I did.

02:01:49 22 Q And did you also analyze additional secondary
02:01:52 23 considerations that Amarin has raised in this case?

02:01:55 24 A Yes, specifically, the REDUCE-IT results.

02:02:03 25 Q What legal standards did you apply in your understanding

1 to analyze secondary considerations?

2 A My understanding is that evidence of secondary
3 considerations must be commensurate in scope with the claims
4 for which the evidence is offered to support, and that there
5 must be a nexus between the evidence of secondary
6 considerations and the merits of the claimed invention.

7 Q And did you apply any legal standards specific to
8 unexpected results and long felt, unmet need?

9 A Yes. So additionally the unexpected results must be
10 different in kind and not merely in degree from the results of
11 the prior art. In other words, there would be a qualitative
12 and not a quantitative difference. And there is no long felt
13 unmet need if others have previously solved the need.

14 Q So turning to DDX 6.147, with snapshots from DX 1591 and
15 DX 1534, let's focus first on the reduction in apo-B.

16 Do you agree were Amarin's argument that an
17 8.5 percent reduction in apo-B was unexpected in March 2008?

18 A I don't. Kurabayashi 2000 showed that the apo-B levels
19 in the EPA group were significantly lower at week 48 compared
20 with the baseline level, and this was by a Nova analysis, and
21 they cite the specific data.

22 You can see that the percent change in the control
23 group at 48 weeks was negative 1.5 percent, which was not
24 significant. In the EPA group, there was a 6.9 percent
25 reduction that was highly significant at the P less than .001

level, and, in my opinion 7 percent and 8.5 percent are not significantly different. That's just a difference in extent, not in kind.

Q So turning to DDX 6.148, does other prior art support your opinion that the reduction in apo-B was expected?

A Yes, the Grimsgaard 1997 publication. I'll note this was a placebo-control study so this was a different way of analyzing the data. So we're seeing it both in terms of a Nova of changes in an individual group, and in comparison to a placebo group here.

And what we're looking at is specifically at the bottom of the chart, an apo-B level that went down by 3 percent, and the P value was significant at less than .05.

I also note that this was a relatively large study with about 75 patients in the group, actually similar to the MARINE study.

Q Is the difference between a 3 percent reduction and an 8.5 percent reduction in apo-B a difference in kind or one in degree?

A In my opinion, it would be a matter of degree.

Q So, in your opinion, is a reduction in apo-B an unexpected result that weighs against obviousness in this case?

A No.

Q Now, turning to DDX 6.149, there's snapshot from DX 1694,

02:05:30 1 page 239, and this is an exhibit that's already admitted into
02:05:34 2 evidence. We've heard some testimony about it today.

02:05:38 3 Is apo-B reduced in all patients who take purified
02:05:45 4 EPA?

02:05:46 5 A No, it's not, and I think that we all know in clinical
02:05:49 6 medicine that there's never a uniform response to any
02:05:52 7 intervention.

02:05:53 8 They actually quantified this in the MARINE study
02:05:56 9 using a method that was described yesterday where they present
02:06:00 10 both a percent change from baseline as a median, but also what
02:06:03 11 are called the Q1 and Q3 intervals.

02:06:07 12 So the usually reported value is the median value so
02:06:11 13 that would be the median value for the whole group, and in the
02:06:14 14 MARINE study, the apo-B levels went down by 4 percent, highly
02:06:21 15 statistically significant.

02:06:23 16 But what they noticed in the Q3 group, and just to
02:06:25 17 remind people what this is, Q1 is the median value of the
02:06:31 18 lower half of the data, and Q3 is the median value of the
02:06:36 19 upper half the data.

02:06:37 20 So this represents the value of the upper
02:06:40 21 50 percentile, about 3 point -- the median value for that was
02:06:44 22 around 3.8, which means, in turn, that about 25 percent of the
02:06:49 23 patients actually had an increase in apo-B levels that was
02:06:52 24 greater than 3.8 percent.

02:06:57 25 Q Now, turning to DDX 6.150, are there asserted claims in

1 this case that are broad enough to cover the treatment of
2 patients whose apo-B is not reduced?

3 A Yes, there are. That would include the '728 claims 1 and
4 16, the '677 claim 1, the '652, claim 1, the '560 claims 4 and
5 17, and the '929 claim 1.

6 Q And turning to DDX 6.151, for the asserted claims you
7 just identified, is the reduction in apo-B that Amarin relies
8 on as a secondary consideration commensurate in scope with
9 those claims?

10 A No, because that would only represent a subset of the
11 total population, and yet they're claiming the benefit for the
12 entire population.

13 Q Did you also analyze the lack of increase in LDL-C in the
14 context of secondary considerations?

15 A Yes, I did.

16 Q So turning to DDX 6.153, do you agree that there was an
17 unmet need in March of 2008 for a treatment that not only
18 reduces triglycerides but also does not increase LDL-C?

19 A I do not.

20 And, first of all, I would like to mention that Mori
21 showed that there could be a significant decrease in
22 triglycerides without an increase in LDL cholesterol with EPA.

23 And I would also like to emphasize that statins were
24 available at this time and could be used to lower LDL
25 cholesterol in patients who had an increase in LDL cholesterol

1 levels.

2 Q Now, in light of Mori, had others previously met any need
3 for reducing triglyceride without increasing LDL-C?

4 A Yes.

5 Q Was there a failure of others to reduce triglycerides
6 without increasing LDL-C?

7 A In my opinion, no.

8 Q Was it unexpected in March of 2008 that purified EPA
9 would reduce triglycerides without increasing LDL-C?

10 A Not in my opinion.

11 Q Was there any relevant scepticism that purified EPA would
12 reduce triglycerides without increasing LDL-C?

13 A No.

14 Q So, in your opinion, does the lack of increase in LDL-C
15 support any secondary considerations that weigh against
16 obviousness?

17 A No.

18 Q Now, turning to DDX 6.154, there are snapshots from
19 DX 1591 at page 10 and DX 1953, page 18, both of which are in
20 evidence.

21 You testified a little bit to this, but was it also
22 possible to counteract the LDL-C increases that were seen with
23 Lovaza using statins?

24 A Yes, of course. Statins are effective at all levels of
25 triglycerides in lowering LDL cholesterol, and this is

1 actually in Amarin's validity contention from another set of
2 communications.

3 They specifically cite -- they specifically state,
4 "The rise in LDL-C was often offset by
5 concurrent treatment with statins. The safety and
6 efficacy of using prescription omega-3s in
7 combination with a statin has been well established."

8 Q And was that -- were those statements in Amarin's
9 validity contentions in this case?

10 A Yes, it was.

11 Q In general, how well do patients tolerate statins?

12 A In my experience, they're extremely well tolerated. In
13 fact, I'd argue that they're one of the best tolerated
14 medications in medicine we have today.

15 Q Turning to DDX 6.155, there's a snapshot on the screen of
16 DX 1581 at page 2. Could you identify this document.

17 A Yes. This is a publication from Medscape which is kind
18 of a magazine that assesses medical findings for the general
19 population as well as for physicians. It's entitled "MARINE:
20 Ethyl-EPA Reduces Triglyceride Levels Without Raising LDL
21 Cholesterol."

22 So specifically here they're quoting Dr. Roger
23 Blumenthal from Johns Hopkins University who I believe is a
24 colleague of Dr. Toth's, and he said, I quote,

25 "That while LDL increases can occur with

1 prescription fish oil or fibrates, the increase is
2 'modest' and 'not that big a deal'."

3 I could -- I could offer an interpretation of
4 why he's saying that, but that would probably be regarded as
5 being speculation so I won't do that.

6 Am I allowed to do that?

7 THE COURT: Well, no, you're not. What's the
8 question, would you redirect?

9 MR. REIG-PLESSIS: I'll ask a question, Your
10 Honor.

11 BY MR. REIG-PLESSIS:

12 Q Does the O'Riordan article support your opinion on the
13 use of statins with Lovaza?

14 A Yes, just to reiterate, he says it's no big deal, the
15 increase is modest. He also mentions that,

16 "The available prescription omega-3 fatty
17 acid is effective in reducing triglycerides, is well
18 tolerated, and, importantly here, works well with
19 statin therapy."

20 In other words, one could readily use a statin
21 to lower LDL cholesterol in this patient population. And he
22 even emphasizes that most patients with high triglycerides
23 have mixed dyslipidemia and would likely be treated with
24 background statin therapy.

25 Q Do you agree with those statements?

02:12:53 1 A Yes, in my experience, that's correct.

02:12:56 2 MR. REIG-PLESSIS: Your Honor, we'd move the
02:12:57 3 admission of DX 1581.

02:12:59 4 MR. SIPES: No objection, Your Honor.

02:13:00 5 THE COURT: 1581 is admitted.

02:13:00 6 (Defendants' Exhibit 1581 received in
02:13:03 evidence.)

02:13:03 7 BY MR. REIG-PLESSIS:

02:13:03 8 Q So turning to DDX .156, there's another snapshot of DX
02:13:09 9 1581 page 2.

02:13:10 10 Do you understand Amarin has relied on statements in
02:13:13 11 the O'Riordan article as evidence for praise for Vascepa's
02:13:18 12 ability to avoid LDL-C increases?

02:13:22 13 A Yes, I do, and they were specifically quoting Dr. Steven
02:13:25 14 Nissen in this particular article where he states,

02:13:29 15 "'It gives you all of the benefit without the
02:13:32 16 downside,' said Nissen. 'It's an interesting
02:13:35 17 wrinkle. There's still room for small companies to
02:13:38 18 do innovative things in this field.'"

02:13:41 19 But even Dr. Nissen had concerns. Specifically
02:13:44 20 he stated that he had concerns about caveats, about the trial
02:13:49 21 size and duration, and that he would like to eventually see a
02:13:53 22 head-to-head comparison between Lovaza -- and this is the
02:13:57 23 prescription omega-3 fatty acid preparation, and AMR 101,
02:14:02 24 which is the EPA preparation that Amarin produces.

02:14:05 25 Q Are you aware of any head-to-head comparison between

02:14:09 1 Lovaza and Vascepa?

02:14:10 2 A I am not.

02:14:13 3 Q In your opinion, does the O'Riordan article support any
02:14:18 4 praise or scepticism with respect to the asserted claims?

02:14:22 5 A I don't believe it does, not in balance.

02:14:30 6 Q So turning to DDX 6.157 with a snapshot of DX 1526, pages
02:14:38 7 15 and 32, which is already in evidence.

02:14:41 8 Even though LDL-C could be reduced with statins, was
02:14:45 9 there still a motivation to improve Lovaza to avoid increases
02:14:50 10 in LDL-C?

02:14:51 11 A Yes, there is. Obviously, patient compliance is a major
02:14:57 12 issue in clinical medicine. For example, most patients
02:15:01 13 prescribed statins don't take them after six months.

02:15:05 14 The more pills you have to take, the more difficult
02:15:08 15 compliance is and the less likely the patients are to use the
02:15:13 16 suggested intervention.

02:15:14 17 It's clearly easier to take one pill, for example,
02:15:19 18 of pure EPA to treat a condition than to combine two pills
02:15:23 19 such as Lovaza with a statin.

02:15:25 20 And this has been long known and widely emphasized.
02:15:29 21 For example, the ATP III guidelines which really center on
02:15:34 22 adherence to LDL-lowering therapy, noticed that it's key to
02:15:38 23 improve adherence by simplifying medication regimens, and
02:15:42 24 that, moreover, they note, drug therapy is a major expense of
02:15:48 25 LDL-lowering therapy, and, in general, it's going to be more

cost-effective to have only one medical intervention as opposed to two.

Q Now, turning to DDX 6.158, there's another snapshot from DX 1694, which is in evidence, page 268. It's the clinical study report for MARINE that we reviewed earlier.

According to MARINE, do all patients taking purified EPA experience the benefit of avoiding increases in LDL-C?

A No, they do not. This is a similar kind of analysis as what was reported earlier for the apo-B when they report the medians and the Q1 and Q3.

So the median decrease in LDL cholesterol in MARINE was about 5 percent, but Q3 indicated that the median value for the top half of the group was a 17 percent increase in LDL cholesterol.

So, in other words, approximately one-quarter of the patients had a greater than 17 percent increase in LDL cholesterol by this analysis.

Q And turning to DDX 6.159, are there asserted claims in this case that are broad enough to cover the treatment of patients who's LDL-C increases?

A Yes, there are. The '929 patent, claim 1, and the '929 patent, claim five.

Q Is the avoidance of increased LDL-C that Amarin relies on commensurate in scope with these claims?

A Not in my opinion.

02:17:30 1 Q Now, do you understand that Amarin is also asserting
02:17:35 2 secondary considerations based on the REDUCE-IT study?

02:17:39 3 A Yes, I do.

02:17:40 4 Q So now on the screen is DDX 6.161 with a snapshot
02:17:50 5 DX 1641, page 9. Could you identify this document.

02:17:53 6 A Yes. This is the Bhatt publication from 2019, the
02:17:58 7 REDUCE-IT study that was published in *The New England Journal*
02:18:03 8 *of Medicine*, one of the two most prestigious journals in
02:18:07 9 clinical medicine.

02:18:08 10 And it describes the results of the REDUCE-IT trial
02:18:10 11 which was a trial of the Amarin EPA preparation in the
02:18:13 12 prevention of coronary artery disease, death, nonfatal MI,
02:18:20 13 that would be a heart attack, nonfatal stroke, coronary
02:18:24 14 revascularization, this is where you put a new vessel in, or
02:18:28 15 you open up a vessel to provide blood flow to the heart, or
02:18:28 16 unstable angina which is chest pain due to ischemia of the
02:18:28 17 heart, i.e., not adequate blood flow.

02:18:37 18 And this study revealed a very significant reduction
02:18:41 19 in cardiovascular risk as defined of 25 percent in patients
02:18:47 20 who received 4 grams of EPA a day.

02:18:50 21 MR. REIG-PLESSIS: And, Your Honor, we move the
02:18:51 22 admission of DX 1641.

02:18:54 23 MR. SIPES: No objection, Your Honor.

02:18:57 24 THE COURT: I thought I saw this article
02:18:59 25 already, but the exhibit is admitted.

02:19:02 1 MR. SIPES: Your Honor, I think the PX version
02:19:04 2 is in. So you'll get two versions.

02:19:06 3 THE COURT: Thank you.

02:19:07 4 MR. REIG-PLESSIS: That's our understanding as
02:19:08 5 well, thank you.

02:19:08 6 (Defendants' Exhibit 1641 received in
02:19:10 evidence.)

02:19:10 7 BY MR. REIG-PLESSIS:

02:19:12 8 Q Now, did you analyze whether there is a nexus between
02:19:15 9 REDUCE-IT and the asserted claims?

02:19:18 10 A I did.

02:19:18 11 Q An what standard did you apply in that analysis?

02:19:22 12 A Well, my understanding is that where the offered
02:19:26 13 secondary consideration actually results from something other
02:19:30 14 than what is both claimed and novel in the claim, there is no
02:19:33 15 nexus to the merit of the claimed invention.

02:19:37 16 In other words, there has to be a connection between
02:19:38 17 the claims and the benefit.

02:19:40 18 Q So did you analyze whether the cardiovascular risk
02:19:45 19 reduction in REDUCE-IT actually results from practicing the
02:19:49 20 asserting the claims?

02:19:50 21 A Yes.

02:19:52 22 Q Turning to DDX 6.163, what is the first limitation of the
02:19:58 23 asserted claims that you analyzed with respect to nexus?

02:20:01 24 A The requirement for a method of reducing triglycerides.

02:20:06 25 Q Does the cardiovascular risk reduction in REDUCE-IT

02:20:10 1 result from a method of reducing triglycerides?

02:20:13 2 A No, it does not, and this is one of the most fascinating
02:20:18 3 observations of this particular paper. The benefit appeared
02:20:22 4 to occur irrespective of the attained triglyceride level at
02:20:27 5 one year.

02:20:28 6 I might mention that JELIS also made this
02:20:31 7 observation which suggests that the cardiovascular risk
02:20:35 8 reduction was not associated with the attainment of a more
02:20:40 9 normal triglyceride level.

02:20:44 10 Q Do any of the asserted claims in this case recite a
02:20:47 11 method of reducing cardiovascular risk?

02:20:50 12 A No.

02:20:50 13 Q Has Amarin obtained patents on reducing cardiovascular
02:20:56 14 risk?

02:20:56 15 A It's my understanding that they have, or at least they're
02:21:00 16 attempting to.

02:21:01 17 Q So turning to DDX 6.164, there's a snapshot on the screen
02:21:06 18 of DX 2001. Could you identify this document.

02:21:11 19 A Yes, this would be U.S. patent 10,278,936 entitled
02:21:19 20 "Methods of Reducing the Risk of Cardiovascular Event in a
02:21:23 21 Subject on Statin Therapy."

02:21:25 22 Let me add that in the REDUCE-IT study all of the
02:21:29 23 subjects were on statins.

02:21:30 24 Q Do you understand this is one of Amarin's patents on
02:21:34 25 methods of reducing cardiovascular risk?

02:21:36 1 A Yes, it specifically states a method of reducing risk of
02:21:40 2 cardiovascular event in a subject on statin therapy.

02:21:44 3 Q Now, is this patent DX 2001, or any other patents on
02:21:49 4 reducing cardiovascular risk, asserted in this case?

02:21:52 5 A No.

02:21:53 6 MR. REIG-PLESSIS: And Your Honor, we move the
02:21:55 7 admission of DX 2001.

02:21:57 8 MR. SIPES: No objection, Your Honor.

02:21:58 9 THE COURT: 2001 is admitted.

02:21:58 10 (Defendants' Exhibit 2001 received in
02:22:02 evidence.)

02:22:02 11 BY MR. REIG-PLESSIS:

02:22:02 12 Q Turning now to DDX 6.165, what is the next limitation of
02:22:08 13 the asserted claims that you analyzed with respect to nexus?

02:22:12 14 A It would be for a subject having fasting triglycerides of
02:22:15 15 at least 500 milligrams per deciliter.

02:22:19 16 Q And, in general, did the REDUCE-IT findings result from
02:22:23 17 treating subjects with triglycerides of at least 500?

02:22:26 18 A In the Bhatt study, eligible patients on a screening exam
02:22:30 19 had to have a fasting triglyceride level of 150 to
02:22:34 20 499 milligrams per deciliter. This is less than
02:22:39 21 500 milligrams per deciliter.

02:22:41 22 Q Now, does the objective of reducing triglycerides below
02:22:45 23 500 have anything to do with reducing cardiovascular risk?

02:22:50 24 A No.

02:22:50 25 Q Do you view severe hypertriglyceridemia as a

cardiovascular disease?

A I review -- I view severe hypertriglyceridemia as being a risk factor for pancreatitis.

Q Now, do you understand that some patients in REDUCE-IT at some point developed triglycerides above 500?

A Yes, and this reflects the fact that triglyceride levels vary over a wide range biologically, and one would expect that if you only had a single determination for a triglyceride value, that one might have a considerably different value on a subsequent determination.

And so if one had a triglyceride value, for example, of 475 initially, one could very easily have a triglyceride level of 525 or 550 on a subsequent determination.

Q And apart from those patients, was REDUCE-IT specifically designed to evaluate patients were triglycerides above 500?

A No, it was not.

Q So turning to DDX 6.166, there is a snapshot from DX 1641, the Bhatt paper on REDUCE-IT, at page 5.

What is the next limitation you analyzed with respect to nexus?

A There was a requirement for a 12-week response.

Q Is there any evidence that the cardiovascular risk reduction in REDUCE-IT occurs within 12 weeks?

A No, there is not. As shown in, again, the Bhatt REDUCE-IT paper published in *The New England Journal of*

02:24:28 1 *Medicine*, they're reporting the cumulative incidence of
02:24:31 2 cardiovascular events.

02:24:32 3 So what we're seeing on the vertical axis, the Y
02:24:36 4 axis, is the hazard ratio -- excuse me, the event rate over
02:24:40 5 time. So the time is indicated on the bottom. The event rate
02:24:44 6 is indicated on the vertical scale. And they're plotting the
02:24:48 7 control group in red, placebo, and the EPA treated group in
02:24:53 8 blue.

02:24:54 9 And what you can see is that there's no divergence
02:24:57 10 between the two groups in terms of cardiovascular risk until
02:25:02 11 year one, and that difference did not become statically
02:25:07 12 significant until year two.

02:25:09 13 Q So now turning to DDX 6.167, there's another snapshot
02:25:15 14 from DX 1641, this time at page 7.

02:25:19 15 What is the next claim limitation you analyzed with
02:25:22 16 respect to nexus?

02:25:23 17 A There was a specific requirement for without
02:25:26 18 substantially increasing LDL-C.

02:25:29 19 Q And did the cardiovascular risk reduction in REDUCE-IT
02:25:33 20 result from the fact that purified EPA does not increase
02:25:36 21 LDL-C?

02:25:37 22 A This is another remarkable finding of this study. There
02:25:41 23 was no relationship to the change in LDL cholesterol levels to
02:25:45 24 the benefit in terms of cardiovascular risk reduction.

02:25:49 25 And, again, this mirrors what was found in the

earlier JELIS study that was published in 2007.

Q And turning to DDX 6.168, with another snapshot from DX 1641, page 2.

What is the next claim limitation you analyzed with respect to nexus?

A Who does not receive concurrent lipid-altering therapy.

Q Did the REDUCE-IT findings result from treating patients who are not on concurrent lipid-altering therapy?

A No. One of the requirements for entry was that they had been receiving a stable dose of statin for at least four weeks prior to entering the trial.

Q So, in your opinion, did the cardiovascular risk reduction in REDUCE-IT actually result from what is claimed in the asserted claims?

A No, it does not.

Q Is there any nexus between the REDUCE-IT results and the asserted claims?

A In my opinion, no.

Q Is there any secondary considerations concerning REDUCE-IT relevant to whether the asserted claims are obvious?

A I don't believe so.

Q Now, regardless of nexus, did the prior art disclose that purified EPA reduces cardiovascular risk?

A It did.

Q So turning to DDX 6.169, theirs is a snapshot from

DX 1553 at page 1.

What prior art reference reported the risk reduction provided by EPA?

A This would be the Yokoyama paper 2007 published in *The Lancet*, the so-called JELIS study.

This is also the same first author that described this study in 2003, and this article reports the results of that, the effects of EPA on major coronary events in JELIS.

And here, specifically they note that patients were randomly assigned to receive either 1.8 grams of EPA daily with a statin, the EPA group, or statin only, the control group.

And the major finding -- and this was the primary endpoint, was a decrease in cardiovascular risk as they defined it, which was very similar to that in REDUCE-IT, of a 19 percent relative reduction in major coronary events, very similar to the 25 percent reduction reported in REDUCE-IT.

And their conclusion and the discussion is that EPA is a promising treatment for the prevention of major coronary events.

Q Was the difference between the 19 percent risk reduction in JELIS and the 25 percent risk reduction in REDUCE-IT a difference in degree or difference in kind?

A A difference in degree. And, in fact, I think from a clinical perspective those are indistinguishable.

Q So turning now to DDX 6.170, there's a snapshot of DX 1641, the Bhatt publication we saw earlier, page 2.

Did the REDUCE-IT investigators acknowledge the findings of JELIS?

A They did. In their own paper they state that JELIS,

"The risk of major coronary events was significantly lower, by 19 percent, in the group that received EPA."

And they further acknowledge that,

"These considerations led to the design of the REDUCE-IT study."

Q So, in your opinion, was REDUCE-IT a confirmatory study?

A Yes. Don't get me wrong, a very nice confirmatory study, but it was a confirmatory study.

Q Turning now to DDX 6.171, there's snapshot on the screen of DX 1836, page 71, and this exhibit is already in evidence.

Could you identify this document.

A Yes, this was a letter from Amarin to the Food and Drug Administration.

Q And in this letter did Amarin make representations to FDA about JELIS?

A Yes. They state,

"JELIS was a very large, well-designed study with blinded endpoint evaluation that demonstrated a statistically significant reduction in CV risk due to

02:30:10 1 statin add-on therapy," in other words, on top of
02:30:12 2 statins.

02:30:13 3 "Amarin believes its results should not be
02:30:16 4 dismissed lightly."

02:30:18 5 And they go on to state, "These points
02:30:21 6 strongly support the consideration of the JELIS study
02:30:24 7 in evaluating the potential CV benefits of Vascepa
02:30:29 8 therapy."

02:30:30 9 Q Are Amarin's statements to FDA consistent with how a
02:30:36 10 person of skill in the art as of March 2008 would have
02:30:37 11 interpreted JELIS?

02:30:38 12 A Yes.

02:30:39 13 Q So turning to DDX 6.172, in light of JELIS, was there an
02:30:46 14 unmet need in March of 2008 for a triglyceride-lowering drug
02:30:51 15 that reduced cardiovascular risk?

02:30:53 16 A In my opinion, no.

02:30:54 17 Q Was there a failure of others to reduce cardiovascular
02:30:58 18 risk with a triglyceride-lowering drug?

02:31:00 19 A No.

02:31:01 20 Q Was it unexpected that purified EPA would reduce
02:31:05 21 cardiovascular risk?

02:31:06 22 A No.

02:31:07 23 Q Was there any relevant scepticism that purified EPA would
02:31:12 24 reduce cardiovascular risk?

02:31:14 25 A In my opinion, no, and that would be based again on the

Yokoyama study published in *Lancet* in 2007 which demonstrated a 19 percent relative reduction in major coronary events, and, as the authors themselves conclude,

"EPA is a promising treatment for the prevention of major coronary events."

Q And as of March of 2008, did persons of skill believe that fish oil could have cardiovascular benefits?

A Yes. I, myself, did.

Q In your opinion, is JELIS the closest prior art to REDUCE-IT?

A Yes.

Q In your opinion, does REDUCE-IT support any secondary considerations that weigh against obviousness?

A No.

Q So turning to DDX 6.173, there are snapshots from DX 1741, the Bays reference, and DX 1641, the Bhatt reference, which are both in evidence.

Do you understand that Amarin has alleged that the secondary considerations you just analyzed are particularly significant for diabetic patients?

A Yes.

Q In the clinical studies that Amarin relies on for secondary considerations, did all of the patients have diabetes?

A No. In the MARINE study, about 28 percent of the

02:32:42 1 subjects had diabetes, and in the Bhatt study, it was about
02:32:47 2 60 percent of the patients that had diabetes. So 40 percent
02:32:50 3 of the patients did not.

02:32:51 4 And I think this is something that hasn't come up
02:32:54 5 adequately in discussions so far, but diabetes is a major
02:32:57 6 factor in terms of risk for elevated triglycerides.

02:33:02 7 Q But are there patients with severe hypertriglyceridemia
02:33:05 8 who are not diabetic?

02:33:07 9 A Yes.

02:33:07 10 Q Are any of the asserted claims in this case limited to
02:33:11 11 treating diabetic patients?

02:33:14 12 A Not that I'm aware of.

02:33:16 13 Q So are any alleged secondary considerations that are
02:33:20 14 specific to diabetic patients, commensurate in scope with the
02:33:25 15 assert claims?

02:33:26 16 A Not in my opinion, no.

02:33:28 17 Q Based on all of the factors that you analyzed, including
02:33:31 18 secondary considerations, what is your ultimate opinion as to
02:33:35 19 whether the asserted claims would have been obvious to a
02:33:39 20 person of skill in the art in March 2008?

02:33:42 21 A I think it would have been obvious to examine EPA and DHA
02:33:47 22 individually for their effects on triglyceride levels and LDL
02:33:51 23 cholesterol levels as well apo-B levels.

02:33:55 24 I think there was abundant evidence that they were
02:33:58 25 appropriate for treating patients with triglyceride levels

02:34:01 1 above 500.

02:34:02 2 I think that there was very strong evidence from the
02:34:04 3 JELIS trial that EPA therapy would have cardiovascular
02:34:08 4 benefit, and, moreover, I think JELIS provided very strong
02:34:14 5 evidence that the cardiovascular benefit observed with EPA was
02:34:19 6 independent of effects on triglyceride lowering or LDL
02:34:25 7 cholesterol lowering.

02:34:26 8 Q Would you opinions with respect to obviousness change in
02:34:29 9 you were analyzing the obviousness as of February 2009?

02:34:32 10 A No.

02:34:34 11 MR. REIG-PLESSIS: No further questions at this
02:34:36 12 time.

02:34:43 13 THE COURT: I wonder if we should continue or
02:34:46 14 take our break. Why don't we take a recess now before -- so
02:34:52 15 you can set up your cross-examination unless you prefer to
02:34:56 16 start.

02:34:57 17 MR. SIPES: Your Honor, happy to do whichever
02:34:59 18 you prefer.

02:35:00 19 THE COURT: Why don't take our brief recess now,
02:35:02 20 thank you.

02:35:03 21 MR. SIPES: Thank you, Your Honor.

02:35:03 22 (A recess was taken.)

02:42:13 23 THE COURT: Please be seated.

02:54:56 24 MR. SIPES: Your Honor, if I may proceed?

02:55:02 25 THE COURT: Yes.

CROSS-EXAMINATION

BY MR. SIPES:

Q Dr. Heinecke, I'm Christopher Sipes on behalf Amarin.
You may recall we met at your deposition.

A I recall very well.

Q Good afternoon. It's good to be here again.

Let me try to -- we've gone through a lot of
literature today so let's try to look at the key prior art
again.

MR. SIPES: Mr. Brooks, if you could turn on
slide DDX 6.13.

BY MR. SIPES:

Q Do you recall this slide, Dr. Heinecke? This is the
slide I think you identified as the key prior art slide.

A Yes.

Q And, in fact, this is four references, it's the Lovaza
PDR, Mori, Hayashi, and Kurabayashi, correct?

A Yes.

Q Not only is it the key prior art, these are the four
references that you used in your combinations to argue
obviousness, correct?

A Correct.

Q And just to clarify the motivation here, the motivation
as you've argued it is for a person of ordinary skill in the
art to modify Lovaza in light of Mori and optionally Hayashi

1 and Kurabayashi, so as to treat very high triglyceride
2 patients using pure EPA, correct?

3 A I'd phrase that slightly differently. I could say that
4 Lovaza was effective at lowering triglycerides but had an
5 undesirable side effect.

6 It had two major components, both of which were
7 known to lower triglycerides, so, in my mind, it would have
8 been obvious to examine each individually to see if they add
9 beneficial as well as deleterious effects.

10 Q But the prior art that you're using for teaching about
11 purified EPA are Mori, Hayashi, and Kurabayashi, correct?

12 A Along with the Lovaza PDR.

13 Q Correct. Well, the Lovaza PDR, to be clear, describes a
14 mixture of omega-3 fatty acids, correct?

15 A Correct.

16 Q The Lovaza PDR does not describe the effects of any
17 particular omega-3 fatty acid.

18 A That's correct.

19 Q Okay. And the undesirable side effect that you mentioned
20 about Lovaza that was the motivating factor here was the rise
21 in LDL-C in patients with severe hypertriglyceridemia?

22 A Yes.

23 MR. SIPES: And then, Mr. Brooks, if we could
24 turn to DDX 6.73.

25

02:57:10 1 BY MR. SIPES:

02:57:17 2 Q And DDX 6.73, you set forth the elements that you think
02:57:21 3 are taught in each of these pieces of key prior art, correct?

02:57:25 4 A Yes.

02:57:25 5 Q And in terms of a teaching of administration patients
02:57:30 6 with triglycerides of 500 or above, the two pieces of prior
02:57:35 7 art are Lovaza and Hayashi correct?

02:57:39 8 A Yes.

02:57:40 9 Q While you've mentioned Kurabayashi, Kurabayashi was not
02:57:42 10 looking at severely hypertriglyceridemia patients, correct?

02:57:46 11 A Correct.

02:57:47 12 Q The Kurabayashi patients were hypercholesterolemic
02:57:52 13 patients, correct?

02:57:53 14 A Yes, mildly hypercholesterolemic.

02:57:55 15 Q Similarly, the Mori reference was not patients with
02:57:59 16 severely high hypertriglyceridemia correct?

02:58:02 17 A Yes.

02:58:02 18 Q In fact, in Mori, the patients had only elevated
02:58:06 19 triglycerides, not even high triglycerides, correct?

02:58:08 20 A I don't recall the specific values, but I'll accept what
02:58:13 21 you said as correct.

02:58:14 22 Q In fact, in Mori they had both elevated triglycerides and
02:58:18 23 elevated cholesterol, correct?

02:58:18 24 A Yes.

02:58:20 25 Q Those are patients that are referred to as mixed

02:58:24 1 dyslipidemic patients, correct?

02:58:25 2 A There's always some issues with nomenclature in the
02:58:31 3 lipoprotein field, but that's oftentimes used.

02:58:33 4 Q And if you'll look at your reply report, DX 1597,
02:58:47 5 paragraph 60, which is on page 22 of the report. I don't have
02:58:54 6 the exhibit number page unfortunately, but it's paragraph 60.

02:58:59 7 You recognize this, Dr. Heinecke, as your reply
02:59:03 8 report, correct?

02:59:09 9 A Yes.

02:59:10 10 Q This was your sworn testimony as of June of 2019,
02:59:14 11 correct?

02:59:15 12 A Yes.

02:59:15 13 Q And you state in paragraph 60 --

02:59:19 14 MR. SIPES: The second paragraph, Mr. Brooks --
02:59:21 15 the second sentence that "begins by contrast."

02:59:21 16 BY MR. SIPES:

02:59:24 17 Q You stated,

02:59:25 18 "By contrast, a POSA would have understood
02:59:28 19 that the second patient population discussed in the
02:59:31 20 Tricor label -- patients with hypertriglyceridemia --
02:59:35 21 are entirely different from patients with
02:59:40 22 hypercholesterolemia and mixed dyslipidemia."

02:59:44 23 Correct? Did I read your testimony from June of
02:59:47 24 2019, correctly?

02:59:47 25 A Yes. What I'm referring here to --

03:00:04 1 Q Dr. Heinecke --

03:00:04 2 A -- specifically is underlying pathogenic mechanisms.

03:00:05 3 Q Dr. Heinecke, you said that the underlying pathogenic
03:00:10 4 mechanisms were different.

03:00:10 5 A That's what I was contending here, yes.

03:00:14 6 Q So in terms -- coming back to it, coming back now to your
03:00:21 7 slides, if we could look at DDX 6.73, again, in terms of
03:00:32 8 patients over 500, patients with severe hypertriglyceridemia,
03:00:36 9 we're looking at Lovaza and Hayashi, and, as we've discussed,
03:00:40 10 Lovaza reports a rise in LDL-C from the mixture.

03:00:43 11 And, I think as you testified, Hayashi, because of
03:00:47 12 the limitations in the study, didn't describe the effects on
03:00:51 13 LDL-C of any patients over 400, correct?

03:00:54 14 A Yes.

03:00:55 15 Q So in terms of the key prior art, there's no description
03:01:01 16 of the effect of pure EPA on patients with severe
03:01:07 17 hypertriglyceridemia.

03:01:08 18 A I think there is evidence that EPA would lower
03:01:14 19 triglycerides in patients with high triglycerides above 500,
03:01:17 20 but there was no direct evidence on LDL cholesterol.

03:01:20 21 Q All right. So it seems to me an issue that's worth
03:01:23 22 discussing this afternoon is what would have been expected
03:01:26 23 about the effects of lowering triglycerides on LDL-C in
03:01:31 24 patients with severe hypertriglyceridemia.

03:01:34 25 But I think maybe before we get there, let's go back

1 a little bit over your background. It's correct, is it not,
2 Dr. Heinecke, that you stopped seeing patients in 2008?

3 A Around 2008 or 2009.

4 Q So -- and in deposition you told me that you can't be
5 sure that you have seen and treated patients with very high
6 triglycerides since 2004, correct?

7 A I said I did not remember treating a specific patient, I
8 believe, at the deposition. I will remind you that was over a
9 decade ago.

10 Q So you say you don't recall now treating severe
11 hypertriglyceridemia since 2004.

12 A I don't recall treating a specific patient, but I was
13 working in a lipid clinic that had a very high percentage of
14 diabetic and hypertriglyceride patients, and I'm quite sure
15 that I did treat some patients with high triglycerides.

16 I'm not as convinced that I treated someone who was
17 undiagnosed chylomicronemia syndrome.

18 Q And similarly --

19 THE COURT: Counsel, I'm going to ask you to
20 pause for a moment. I keep hearing this odd scratchy noise.
21 Miss Clerk is going to find out what's going on.

22 THE WITNESS: Oh, I'm sorry, that's me. I
23 apologize, Your Honor. I'm getting a little agitated over
24 here.

25 THE COURT: All right.

03:02:51 1 MR. SIPES: I'm doing my best, Your Honor. I
03:02:53 2 don't mean to agitate any one.

03:02:55 3 THE COURT: Perhaps you should take a deep
03:02:58 4 breath between each sentence. That would also help the court
03:03:02 5 reporter.

03:03:02 6 All right. Let's resume.

03:03:05 7 BY MR. SIPES:

03:03:05 8 Q And, similarly, you testified at deposition, did you not,
03:03:08 9 that it was not your practice to use Lovaza?

03:03:10 10 A That's correct. In the lipid clinic at the University of
03:03:14 11 Washington we regarded Lovaza as being a very high-priced
03:03:18 12 pharmaceutical drug that could be substituted with generic
03:03:21 13 fish oil which was documented to be equally effective at
03:03:25 14 lowering triglycerides.

03:03:26 15 Q In fact, at deposition you told me had no recollection of
03:03:30 16 prescribing Lovaza.

03:03:31 17 A That's correct.

03:03:32 18 Q And, similarly, you told me you don't recall ever
03:03:35 19 prescribing Vascepa.

03:03:36 20 A Well, this is prior to 2008?

03:03:39 21 Q (Nodding head affirmatively.)

03:03:40 22 A Yeah, no, I have no recollection.

03:03:42 23 Q And just to go through all the omega-3 products, you have
03:03:45 24 no recollection of prescribing Epanova, correct?

03:03:59 25 A No, I do not.

03:04:00 1 Q The question was, and you have no recollection of
03:04:04 2 prescribing Epanova.

03:04:06 3 A I do not.

03:04:07 4 Q And you have no recollection of prescribing Omtric.

03:04:07 5 A I do not.

03:04:07 6 Q Which means you have no recollection of prescribing any
03:04:11 7 of the omega-3 fatty acid products that are currently approved
03:04:17 8 by FDA for lowering triglycerides in persons with severe
03:04:21 9 hypertriglyceridemia.

03:04:21 10 A As I mentioned before, it was my clinical practice, as
03:04:25 11 well as that of my colleagues at the University of Washington,
03:04:28 12 to use generic fish oil because, in our opinion, it was
03:04:32 13 equally effective at lowering triglycerides as the
03:04:36 14 prescription drugs and it was much less expensive for the
03:04:39 15 patients. So that's correct.

03:04:41 16 Q And you do not have a board certification in cardiology.

03:04:45 17 A I'm board certified in endocrinology and metabolism, and
03:04:45 18 I hold the Karasinski Chair in metabolic research at the
03:04:45 19 University of Washington.

03:04:55 20 Q Again, my question was you do not have a board
03:04:57 21 certification in cardiology.

03:04:58 22 A I do not.

03:04:59 23 Q And you do not hold yourself out to patients as a
03:05:01 24 cardiologist.

03:05:02 25 A I hold myself out to be expert in lipoprotein metabolism,

03:05:09 1 physiology, and pathogenesis of atherosclerosis.

03:05:09 2 Q So that would be no, you don't hold yourself out to
03:05:12 3 patients as a cardiologist.

03:05:13 4 A Correct.

03:05:13 5 Q Okay. And you do not consider yourself an expert in
03:05:16 6 cardiology.

03:05:16 7 A I consider myself an expert in preventive cardiology from
03:05:20 8 the perspective of lipoproteins and lipid metabolism.

03:05:25 9 Q But you do not --

03:05:27 10 A Let me just elaborate on that. There's obviously
03:05:29 11 overlaps between the two fields, so I think that you're
03:05:32 12 focusing on the cardiology designation to the exclusion of the
03:05:36 13 fact that what we're focusing on here is lipoproteins and
03:05:40 14 lipoprotein metabolism which is the relevant comparison, not
03:05:43 15 plumbing on somebody who is having acute coronary syndrome.

03:05:48 16 MR. SIPES: Mr. Brooks, if you could play the
03:05:54 17 transcript, just 12 to 14.

03:05:54 18 (Deposition video recording played.)

03:05:57 19 THE WITNESS: Thank you. I'm not expert in
03:05:59 20 cardiology excepting from the perspective of preventive
03:06:02 21 cardiology.

03:06:03 22 BY MR. SIPES:

03:06:03 23 Q You referred to generic fish oil. Did you mean -- in
03:06:10 24 terms of prescribing habits. Did you mean generic Lovaza?

03:06:11 25 A No. I actually meant -- fish oil was and is commercially

03:06:15 1 available.

03:06:16 2 Our practice at the University of Washington was to
03:06:19 3 ask patients to -- excuse me, select a single provider of fish
03:06:25 4 oil that was commercially available without a prescription,
03:06:29 5 and to use that to treat their high triglyceride levels.

03:06:32 6 Q So when you were referring to generic fish oil, you mean
03:06:32 7 fish oil dietary supplements.

03:06:37 8 A Correct.

03:06:38 9 Q You referred in your testimony to the ATP III, correct?

03:06:43 10 A Yes.

03:06:43 11 Q And if you'll look at DX 1876 --

03:06:48 12 MR. SIPES: The first page, Mr. Brooks, and just
03:06:51 13 blow up the title so at least we know what we're talking
03:06:51 14 about.

03:06:51 15 BY MR. SIPES:

03:06:54 16 Q ATP III is the shorthand name for the third report of the
03:06:57 17 National Cholesterol Education Program Expert Panel on
03:07:01 18 Detection, Evaluation, and Treatment of High Blood Cholesterol
03:07:05 19 in Adults (Adult Treatment Panel III) Final Report, correct?

03:07:11 20 A Yes.

03:07:12 21 Q And it's universally referred to as ATP III in part
03:07:16 22 because otherwise the title is just a mouthful, correct?

03:07:19 23 A I would agree with that.

03:07:20 24 Q And the ATP III was put out in part through sponsorship
03:07:24 25 of the NIH, correct?

03:07:26 1 A I would assume that's correct.

03:07:28 2 Q And it was an authoritative source for -- to people of
03:07:34 3 ordinary skill in the art in 2008 for lipid disorders
03:07:34 4 including hypertriglyceridemia and severe
03:07:41 5 hypertriglyceridemia, correct?

03:07:42 6 A I would say it was one source of information that was
03:07:45 7 widely regarded.

03:07:46 8 Q All right. It was a -- it was a very highly-reputed
03:07:51 9 source, correct?

03:07:52 10 A Yes.

03:07:52 11 Q And if you'll turn to page 00181 of ATP III.

03:08:06 12 That's not what I want. I want -- I'm sorry, 177.

03:08:13 13 MR. SIPES: In the left-hand column, if we can
03:08:15 14 blow it up, it refers to elevated triglycerides, and then a
03:08:18 15 chart with a classification, if we can blow that up,
03:08:22 16 Mr. Brooks.

03:08:22 17 BY MR. SIPES:

03:08:23 18 Q And ATP III sets forth a classification of disorders of
03:08:27 19 elevated triglycerides, correct?

03:08:29 20 A Yes.

03:08:30 21 Q And it defines -- ATP III defines very high triglycerides
03:08:35 22 as 500 or above, correct?

03:08:37 23 A Yes.

03:08:40 24 Q And that's what's also known as severe
03:08:44 25 hypertriglyceridemia, correct?

03:08:45 1 A Yes.

03:08:45 2 Q And this -- a person of ordinary skill in the art in 2008
03:08:49 3 would have recognized very high triglycerides or severe
03:08:53 4 hypertriglyceridemia as the condition as defined in ATP III as
03:08:58 5 having triglycerides of 500 or above, correct?

03:09:01 6 A I think that that's one reasonable definition. There are
03:09:05 7 actually other definitions available at that time, but I think
03:09:08 8 this is widely accepted as being one.

03:09:10 9 Q And the ATP III definition was the definition that was
03:09:14 10 used at the time by FDA in terms of approving drugs for
03:09:19 11 treatment of severe hypertriglyceridemia.

03:09:21 12 A Yes.

03:09:21 13 Q So, for example, the ATP classification was used both for
03:09:26 14 the Lovaza approval and the Vascepa approval, correct?

03:09:30 15 A Yes.

03:09:31 16 Q And a person of ordinary skill in the art interested in
03:09:35 17 developing a new treatment for severe hypertriglyceridemia in
03:09:38 18 March of 2008 similarly would have recognized the ATP III
03:09:42 19 definition of severe hypertriglyceridemia as important for
03:09:45 20 purposes of developing a treatment, correct?

03:09:48 21 A Yes.

03:09:48 22 Q Now, if you'll turn to page 00179, table --

03:10:10 23 MR. SIPES: In the left-hand column, Mr. Brooks,
03:10:13 24 there's a table VII.2.2.

03:10:13 25

03:10:13 1 BY MR. SIPES:

03:10:16 2 Q Do you see that? The title there is *Relationship of*
03:10:19 3 *Elevated Triglycerides to Coronary Heart Disease and Other*
03:10:24 4 *Conditions?* Do you see that?

03:10:25 5 A Yes, I do.

03:10:26 6 Q And for -- if we can blow up very high triglycerides and
03:10:29 7 the association, it's the bottom category.

03:10:31 8 A Yes.

03:10:32 9 Q ATP III reports that very high triglycerides is
03:10:36 10 associated with metabolic syndrome, type 2 diabetes, and
03:10:42 11 increased risk for coronary heart disease common. Correct?

03:10:47 12 A Yes.

03:10:47 13 Q And so a person with ordinary skill in the art in 2008
03:10:51 14 would have recognized severe hypertriglyceridemia as
03:10:53 15 associated with metabolic syndrome, type 2 diabetes, and an
03:10:59 16 increased risk for coronary heart disease, correct?

03:11:02 17 A Yes.

03:11:03 18 Q And then if we turn to page 181, which is table VII.2.4,
03:11:12 19 these are the -- at the very top it says Treatment
03:11:15 20 Considerations For Elevated Serum Triglycerides. Do you see
03:11:19 21 that?

03:11:19 22 A Yes, I do.

03:11:20 23 Q And, again, there's a separate set of treatment
03:11:22 24 considerations for very high triglycerides, correct?

03:11:25 25 A Could you go back, please?

03:11:29 1 Q To the top?

03:11:30 2 A To the full table.

03:11:31 3 Q The full table, yes.

03:11:34 4 A What's the question again?

03:11:35 5 Q There's category of treatment considerations for very
03:11:39 6 high triglycerides, correct?

03:11:40 7 A Yeah. There's several categories here, borderline high
03:11:45 8 triglycerides, high triglycerides, and very high
03:11:48 9 triglycerides.

03:11:48 10 Q So let's look at the very high triglyceride treatment
03:11:52 11 considerations.

03:11:53 12 There it reports that for the LDLC of therapy that
03:11:56 13 the first priority is that -- triglyceride lowering to prevent
03:11:59 14 acute pancreatitis, correct?

03:12:01 15 A Yes.

03:12:01 16 Q And then the second goal -- secondary -- second priority
03:12:05 17 is prevent of coronary heart disease, correct?

03:12:09 18 A Yes.

03:12:10 19 Q Now, it goes on to say that statins are not first-line
03:12:13 20 agents for very high triglycerides, "(statins not powerful
03:12:18 21 triglyceride-lowering drugs)." Do you see that?

03:12:21 22 A The ATP III guidelines were released in 2003, is that
03:12:25 23 correct?

03:12:26 24 Q Well, I --

03:12:27 25 A Yes.

03:12:28 1 Q I believe it's 2002, but --

03:12:31 2 A Okay, 2002. So the preparation of that document would
03:12:35 3 have been probably prior to that publication date by quite a
03:12:38 4 significant amount.

03:12:40 5 I would point out that when this report was
03:12:44 6 written -- I'm making the assumption that it took some time to
03:12:47 7 prepare the report.

03:12:48 8 Atorvastatin was not yet on the market, and that was
03:12:53 9 the first drug released that was very high potency that
03:12:55 10 subsequently was shown to very effectively reduce triglyceride
03:12:58 11 levels as monotherapy.

03:12:59 12 Q My question was what ATP III says, and it says that
03:13:04 13 statins are not first-line therapy. It is correct, is it not,
03:13:06 14 Dr. Heinecke, that statins are not approved to treat very high
03:13:09 15 triglycerides?

03:13:10 16 A It's correct that it's not approved, but it's not correct
03:13:13 17 that it's not an effective therapy for lowering very high
03:13:17 18 triglycerides.

03:13:21 19 Q And then if you'll go down to the last bullet under
03:13:25 20 treatment considerations for very high triglycerides, it says,
03:13:28 21 "triglyceride lowering to prevent coronary heart disease."

03:13:32 22 Do you see that?

03:13:33 23 A Yes.

03:13:33 24 Q And,

03:13:33 25 "Efficacy of drug therapy to prevent coronary

03:13:38 1 heart disease in persons with very high triglycerides
03:13:40 2 not demonstrated by clinical trials," correct?

03:13:51 3 A I'm having a little trouble interpreting exactly what
03:13:55 4 that means. Could you give me what you think the
03:13:57 5 interpretation is?

03:13:58 6 Q Actually, I'm trying to ask you questions, Dr. Heinecke.

03:14:01 7 The statement is,
03:14:01 8 "Efficacy of drug therapy to prevent coronary
03:14:01 9 heart disease in persons with very high triglycerides
03:14:06 10 not demonstrated by clinical trials."

03:14:08 11 Correct?

03:14:08 12 A Yes. Okay. I would agree with that.

03:14:09 13 So I think what they're saying is that there's no
03:14:12 14 evidence that treating very high triglycerides lowers
03:14:15 15 cardiovascular risk.

03:14:16 16 Q Right. In fact, that was true even in 2008, correct?

03:14:21 17 A Yes.

03:14:22 18 Q But it's not true today.

03:14:29 19 A I'm not sure I would agree with that statement.

03:14:32 20 Q Would you agree that the efficacy of Vascepa to reduce
03:14:37 21 cardiovascular risk in persons with severe
03:14:40 22 hypertriglyceridemia was finally demonstrated in the REDUCE-IT
03:14:44 23 trial?

03:14:44 24 A I would have to go back and look at that data. There was
03:14:47 25 a very small number of people that were in the triglyceride

03:14:50 1 greater than 500 level. So I can't comment on that
03:14:56 2 specifically.

03:14:57 3 There was --

03:14:58 4 Q Let's see if I can help you, Dr. Heinecke.

03:15:00 5 A Yes.

03:15:01 6 MR. SIPES: Let's pull up PX 207. This is
03:15:04 7 defendants' labeling from before REDUCE-IT.

03:15:08 8 And, Mr. Brooks, could you pull up the
03:15:10 9 limitation of use under highlights of the indications and
03:15:13 10 usage section. You'll see there's two bullets there, and if
03:15:16 11 you could highlight the second bullet under limitations of
03:15:20 12 use.

03:15:20 13 BY MR. SIPES:

03:15:21 14 Q So you see this is the defendants' labeling for the
03:15:23 15 treatment of severe hypertriglyceridemia as of January 2017.
03:15:26 16 Do you see that, Dr. Heinecke?

03:15:27 17 A Could you go back just a step? So whose -- whose label
03:15:32 18 is this?

03:15:33 19 Q Dr. Reddy's Laboratories labeling. They're all
03:15:37 20 substantively identical, but we need to use one of them.

03:15:41 21 A Okay. I'll accept that this is Dr. Reddy's labeling.

03:15:45 22 Q And you recognize --

03:15:45 23 THE COURT: Dr. Heinecke, would it help you to
03:15:47 24 have a physical copy of --

03:15:50 25 MR. SIPES: I think there is one --

03:15:51 1 THE WITNESS: No, I can read it.

03:15:51 2 (Simultaneous indecipherable
03:15:53 conversation.)

03:15:53 3 MR. SIPES: If it would easier one, there's in
03:15:55 4 your binder in front of you.

03:15:57 5 THE WITNESS: I can read it. It's just kind of
03:15:59 6 blurry there.

03:16:00 7 BY MR. SIPES:

03:16:00 8 Q Okay. And do you recognize --

03:16:02 9 MR. SIPES: Mr. Brooks, if you could -- go back
03:16:04 10 to the full -- just blow up icosapent ethyl.

03:16:04 11 BY MR. SIPES:

03:16:10 12 Q You recognize icosapent ethyl as the generic name for
03:16:12 13 Vascepa, correct?

03:16:13 14 A Yes. I prefer to call it EPA, but, yes.

03:16:15 15 Q I prefer EPA, too.

03:16:19 16 THE COURT: I prefer EPA as well.

03:16:19 17 THE WITNESS: We all prefer EPA, we all agree on
03:16:22 18 one thing here.

03:16:23 19 MR. SIPES: And then if you'll look under
03:16:24 20 limitations of use, and, Mr. Brooks, you can pull up --

03:16:24 21 BY MR. SIPES:

03:16:26 22 Q And just to be clear, this is seeking treatment just for
03:16:29 23 severely hypertriglyceridemia patients, correct?

03:16:32 24 A That's what the document states.

03:16:34 25 Q Yeah. And if you look at the second limitation of use --

03:16:37 1 and, again, you'll see this is January 2017. This is before
03:16:40 2 REDUCE-IT. The date is in the lower right-hand column.

03:16:45 3 A Okay.

03:16:46 4 Q There's a limitation of use that reads,

03:16:49 5 "The effect of icosapent ethyl capsules on
03:16:52 6 cardiovascular" risk -- "cardiovascular mortality and
03:16:55 7 morbidity in patients with severe
03:16:58 8 hypertriglyceridemia has not been determined."

03:17:01 9 Do you see that?

03:17:01 10 A I agree. That's what it states.

03:17:03 11 MR. SIPES: Okay. And then, Mr. Brooks, if
03:17:06 12 you'll turn to page 2.

03:17:07 13 The limitation of use under indication of usage,
03:17:11 14 there's that very same indication for use, correct?

03:17:17 15 A Yes.

03:17:18 16 MR. SIPES: And then if we go to the clinical
03:17:21 17 study section, section 14, Mr. Brooks. The next page,
03:17:28 18 Mr. Brooks. The -- right at the bottom. Right there.

03:17:28 19 BY MR. SIPES:

03:17:32 20 Q You'll see it says once again in the clinical study
03:17:34 21 section,

03:17:35 22 "The effect of icosapent ethyl on
03:17:36 23 cardiovascular mortality and morbidity in patients
03:17:40 24 with severe hypertriglyceridemia has not been
03:17:42 25 determined."

03:17:42 1 Do you see that?

03:17:43 2 A Yes, I do.

03:17:44 3 Q So three times in the labeling it cautions that the
03:17:49 4 effect of icosapent ethyl, which is EPA, on cardiovascular
03:17:53 5 mortality and morbidity in patients with severe
03:17:58 6 hypertriglyceridemia has not been determined, correct?

03:17:59 7 A That's what this document states.

03:18:04 8 MR. SIPES: Your Honor, I move PX 207 into
03:18:07 9 evidence.

03:18:08 10 MR. REIG-PLESSIS: No objection, your Honor.

03:18:10 11 MR. SIPES: Now let's take --

03:18:10 12 THE COURT: 207 is admitted.

03:18:10 13 (Plaintiffs' Exhibit 207 received in
03:18:10 14 evidence.)

03:18:13 14 MR. SIPES: Now let's take a look at Dr. Reddy's
03:18:15 15 Laboratories' labeling post REDUCE-IT. Mr. Brooks, if you
03:18:20 16 could pull up PX 1209. If you'll just --

03:18:20 17 BY MR. SIPES:

03:18:27 18 Q You'll see this is the labeling for icosapent ethyl
03:18:31 19 capsules as of January 2020, do you see that?

03:18:33 20 A Yes.

03:18:34 21 Q And, again, the sole indication here is for the treatment
03:18:40 22 of severe hypertriglyceridemia, correct?

03:18:43 23 A I don't -- I can't see it. You're going to have to help
03:18:48 24 me. Could you outline it for me, please.

03:18:49 25 MR. SIPES: Mr. Brooks, if we can outline --

03:18:51 1 above there, right under indications and usage. There we go.

03:18:51 2 BY MR. SIPES:

03:18:59 3 Q You see indications and usage in the left-hand corner?

03:19:03 4 A Yes, I do.

03:19:04 5 Q And it's as an adjunct to diet to reduce TG levels in
03:19:09 6 adult patients with severe hypertriglyceridemia, correct?

03:19:12 7 A Yes, I see that.

03:19:14 8 Q That's the sole indication there, correct?

03:19:15 9 A Yes. I'll point out that the indication for treating
03:19:18 10 severe hypertriglyceridemia is to avoid the risk of
03:19:22 11 pancreatitis, not to lower the risk for cardiovascular
03:19:25 12 disease.

03:19:25 13 Q Now, interestingly, there's a limitation of use that the
03:19:28 14 effect of icosapent ethyl capsules on the risk for
03:19:31 15 pancreatitis in patients with severe hypertriglyceridemia has
03:19:34 16 not been determined, correct?

03:19:39 17 A Yes, that's what it states.

03:19:42 18 Q But what's gone now is the limitation of use that the
03:19:45 19 effect on a cardiovascular risk has not been determined.

03:19:51 20 A State that again, please?

03:19:53 21 Q The limitation of use that we saw in the pre-REDUCE-IT
03:19:57 22 labeling, that the effect of icosapent ethyl on cardiovascular
03:20:00 23 risk in severe hypertriglyceridemia patients has not been
03:20:06 24 determined, that limitation of use has been removed.

03:20:08 25 A Yes.

03:20:09 1 Q And if we go to the next page for indications and usage,
03:20:15 2 it's gone from there as well, correct?

03:20:24 3 A Yes.

03:20:25 4 Q And if we go to the clinical studies section, next
03:20:33 5 page --

03:20:34 6 A I'll take your word for it.

03:20:36 7 Q It's gone from there.

03:20:37 8 So FDA has found based on REDUCE-IT that EPA reduces
03:20:44 9 cardiovascular risk in patients with severe
03:20:47 10 hypertriglyceridemia, correct?

03:20:49 11 MR. REIG-PLESSIS: Objection, Your Honor, calls
03:20:50 12 for speculation, lack of foundation.

03:20:53 13 MR. SIPES: Your Honor, he has been talking
03:20:54 14 about the teachings of an enormous amount of literature and
03:20:59 15 reading labels and opining on labels in his report, and now
03:21:03 16 they're saying he can't say what's going on with the labeling
03:21:06 17 here?

03:21:06 18 THE COURT: I agree with Mr. Sipes. The
03:21:08 19 objection is overruled. Would you ask him the question again.

03:21:12 20 BY MR. SIPES:

03:21:12 21 Q So FDA has determined, based on REDUCE-IT, that the
03:21:16 22 effect of EPA on cardiovascular risk in patients with severe
03:21:20 23 hypertriglyceridemia has been determined.

03:21:22 24 A I'll accept that as being correct.

03:21:24 25 Q Okay.

03:21:27 1 A But I would like to mention again that the goal of
03:21:31 2 treating triglycerides above 500 milligrams per deciliter is
03:21:37 3 to prevent pancreatitis.

03:21:38 4 The goal of preventing coronary artery disease is a
03:21:42 5 secondary consideration. The treatment of high triglycerides
03:21:45 6 above 500 is an acute event. It typically can be carried out
03:21:50 7 over a relatively quick period of time, whereas the reduction
03:21:54 8 of cardiovascular risk as demonstrated in JELIS and in
03:21:57 9 REDUCE-IT requires several years of therapy.

03:22:00 10 So, in my opinion, I'm -- I don't think this is a
03:22:04 11 major issue. You're not going to be using EPA to lower
03:22:07 12 triglycerides above 500 in order to reduce cardiovascular
03:22:12 13 risk. That's not what any clinician would do.

03:22:15 14 Q Would you view the reduction of heart attacks and strokes
03:22:18 15 in severely hypertriglyceridemic patients as an additional
03:22:22 16 beyond reducing triglycerides as desirable?

03:22:25 17 A I think, again, it's in a different context.

03:22:28 18 One is an acute setting where one needs to reduce
03:22:32 19 triglycerides rapidly. The other is a long-term treatment
03:22:35 20 protocol where many different approaches could be used.

03:22:39 21 Yes, ideally, of course, that would be necessary,
03:22:41 22 but I think you're confounding things here.

03:22:44 23 Q No.

03:22:45 24 A I think you're confounding cardiovascular risk reduction
03:22:48 25 over many years of treatment with acute reduction in risk of

03:22:52 1 pancreatitis.

03:22:53 2 Q Some patients with very high triglycerides have a chronic
03:22:58 3 condition that will require being on TG lowering indefinitely,
03:23:01 4 potentially for their whole lives, correct?

03:23:04 5 A Correct.

03:23:05 6 Q Okay. And those patients certainly now have an
03:23:09 7 additional benefit, correct?

03:23:12 8 A Well, I think it depends on the context of the situation.

03:23:15 9 For example, the classic example of very high
03:23:17 10 triglycerides is LPL deficiency where patients have very, very
03:23:22 11 high triglycerides, and, in this clinical setting, EPA and
03:23:26 12 omega-3 fatty acids are ineffectual.

03:23:28 13 So I think you're making broad generalizations that
03:23:32 14 are not justified by the clinical data.

03:23:35 15 Q The drugs approved by FDA to treat very high
03:23:41 16 triglycerides are fibrates, niacin, Lovaza, Epanova, Omtric,
03:23:47 17 and Vascepa, correct?

03:23:48 18 A Yes.

03:23:49 19 Q The only one of those drugs to show a cardiovascular
03:23:54 20 benefit on top of a statin is Vascepa.

03:23:57 21 A Yes.

03:23:58 22 Q The only one of those drugs that has been shown that it
03:24:02 23 can be administered to very high triglycerides patients to
03:24:05 24 reduce triglycerides without raising LDL-C is Vascepa,
03:24:09 25 correct?

03:24:09 1 A Correct.

03:24:13 2 But I would actually argue, in my opinion, if I saw
03:24:17 3 a patient with very high triglycerides, I would -- I would use
03:24:22 4 fish oil or Lovaza or EPA to reduce the triglycerides to a
03:24:26 5 level where they were not at risk of pancreatitis. At that
03:24:29 6 point my management would change to consider cardiovascular
03:24:33 7 risk.

03:24:34 8 So, again, I think you're confounding reducing the
03:24:36 9 acute risk for pancreatitis with long-term cardio prevention.

03:24:42 10 Q Did I understand your testimony on direct to be that it
03:24:45 11 takes some time to be administered EPA before the reduction in
03:24:50 12 cardiovascular risk occurs?

03:24:52 13 A Yes.

03:24:53 14 Q Is it better to start sooner or later?

03:24:56 15 A Well, first of all, you understand that cardiovascular
03:25:01 16 disease is a long-term process. There is no divergence in the
03:25:06 17 JELIS trial -- excuse me, in the REDUCE-IT trial until after
03:25:10 18 two years of therapy.

03:25:11 19 The notion that one month or two months difference
03:25:14 20 in treatment for cardiovascular risk is going have any
03:25:18 21 clinical significance in my mind is not a fair interpretation
03:25:23 22 of what's going on here clinically.

03:25:25 23 Q Lovaza, in severely hypertriglyceridemia patients,
03:25:30 24 produced a median placebo adjusted LDL-C increase of almost
03:25:36 25 50 percent, correct?

03:25:37 1 A Yes.

03:25:37 2 Q Tricor -- which is Fenofibrate, correct?

03:25:43 3 A Yes.

03:25:43 4 Q Tricor produced an increase in LDL-C in severely
03:25:51 5 hypertriglyceridemia patients compared to placebo of, again,
03:25:55 6 almost 50 percent, correct?

03:25:56 7 A Yes, but I'll point out that high potency statins can
03:26:00 8 lower both triglycerides and LDL cholesterol in the same
03:26:04 9 setting. They're not approved by the FDA, but they will do
03:26:07 10 the same thing, and they're widely used for that clinically.

03:26:10 11 Q But looking here at the TG lowering medications that are
03:26:13 12 approved for the treatment of very high triglycerides, both
03:26:16 13 Tricor, which is Fenofibrate, and Lovaza increase LDL-C by
03:26:21 14 about 50 percent, correct?

03:26:22 15 A Yes.

03:26:23 16 Q Now, let me ask you to take look at the Carlson paper
03:26:27 17 which is PX 1026.

03:26:32 18 The Carlson paper is a paper entitled "On the Rise
03:26:35 19 in Low Density and High Density Lipoproteins In Response to
03:26:39 20 the Treatment of Hypertriglyceridemia in Type IV and Type V
03:26:44 21 Hypolipoproteinemias" in the *Journal of Atherosclerosis* from
03:26:49 22 1977, correct?

03:26:50 23 A Yes, it is.

03:26:50 24 Q The Carlson 1997 paper is part of the prior art, correct?

03:26:54 25 A Yes, it is.

03:26:55 1 MR. SIPES: I would move PX 1026 into evidence.

03:26:58 2 MR. REIG-PLESSIS: No objection.

03:27:00 3 THE COURT: 1026 is admitted.

03:27:00 4 (Plaintiffs' Exhibit 1026 received in
03:27:05 evidence.)

03:27:05 5 BY MR. SIPES:

03:27:05 6 Q And Carlson examined the effects of niacin in persons
03:27:08 7 with very high triglycerides, correct?

03:27:10 8 A That's what the title states.

03:27:13 9 MR. SIPES: And, in fact, if we look,
03:27:14 10 Mr. Brooks, at PX 1026-0003, it says at the top, if you look
03:27:31 11 at under Results, Mr. Brooks?

03:27:31 12 BY MR. SIPES:

03:27:31 13 Q It says,

03:27:37 14 "The data from our first report on the
03:27:40 15 striking increases in both LDL and HDL cholesterol
03:27:40 16 and phospholipids when the raised levels of VLDL (and
03:27:50 17 chylomicrones) are reduced in Type V HLP as shown in
03:27:54 18 Figure 2."

03:27:54 19 Do you see that?

03:27:59 20 A Yes, I see that.

03:28:00 21 Q And then the next paragraph repeats again,

03:28:04 22 "...the rise in LDL and HDL cholesterol is a
03:28:07 23 general phenomenon when Type V HLP is treated is
03:28:12 24 apparent from the results of nine patients with Type
03:28:16 25 V HLP who were treated with diet alone or with

03:28:19 1 nicotinic acid. All four patients treated with diet
03:28:19 2 and all five treated with nicotinic acid had
03:28:19 3 pronounced increases in LDL cholesterol when VLDL
03:28:33 4 fell towards normal values and all but two had
03:28:33 5 increases in HDL cholesterol."

03:28:35 6 Correct? That's what they cite?

03:28:36 7 A That's what they state.

03:28:37 8 Q And I have trouble saying the word, but Type V
03:28:41 9 hyperlipoproteinemias that's being referred to with Carlson,
03:28:44 10 that's very high triglycerides, correct?

03:28:46 11 A That reflects the accumulation of both VLDL and
03:28:51 12 chylomicron particles in the blood, yes.

03:28:53 13 Q So those are patients with severe hypertriglyceridemia,
03:28:58 14 correct?

03:28:58 15 A Yes.

03:28:59 16 Q And Carlson refers to the rise in LDL in reducing
03:29:03 17 triglycerides as a general phenomenon, correct?

03:29:07 18 A When was this paper published?

03:29:09 19 Q Dr. Heinecke, if you could answer my question.

03:29:13 20 A That's what they refer to it as.

03:29:16 21 Q And the observation that it is a general phenomenon comes
03:29:19 22 from their observation that LDL goes up in severely
03:29:23 23 hypertriglyceridemic patients when you reduce triglycerides
03:29:26 24 either with niacin or with diet.

03:29:28 25 A I think you're taking this out of context. They're

03:29:33 1 making very broad statements based on -- what was it? Four
03:29:36 2 patients?

03:29:37 3 And, actually, I remember looking at this paper, and
03:29:39 4 I couldn't find a report of what the triglyceride levels were
03:29:43 5 in the patients actually.

03:29:45 6 They claim that they're Type V hyperlipidemic
03:29:50 7 patients, but I didn't see actual documentation of that in the
03:29:53 8 paper.

03:29:54 9 And I also believe this paper was published quite
03:29:56 10 some time ago, and, moreover, I would argue that this reflects
03:29:59 11 a very naive understanding of lipoprotein metabolism and
03:30:03 12 what's going on under these conditions.

03:30:05 13 Q But to be clear, just trying to understand what the paper
03:30:08 14 is saying, I understand you've got your criticisms of this
03:30:11 15 paper, they viewed the rise in LDL-C from reducing
03:30:15 16 triglycerides in severely hypertriglyceridemic patients as a
03:30:19 17 general phenomenon because it occurred, not just from the drug
03:30:23 18 niacin, but also from diet alone, correct?

03:30:28 19 I'm asking what they were reporting, Doctor?

03:30:30 20 A That may be what they reported. I don't agree with their
03:30:34 21 assessment.

03:30:35 22 MR. SIPES: Okay. Well, let's look at a later
03:30:40 23 analysis. Mr. Brooks, if you could pull up PX 754, and just
03:30:49 24 the top of it first.
03:30:49 25

03:30:49 1 BY MR. SIPES:

03:30:50 2 Q So these are the reports of an expert panel that Amarin
03:30:54 3 convened in December 2008, and one of the experts was Michael
03:31:00 4 Criqui. Are you familiar with Michael Criqui?

03:31:03 5 A I am not.

03:31:04 6 Q And if we go to the next page. Well, first it says he's
03:31:07 7 professor of preventive medicine at the University California.
03:31:11 8 Are you familiar with the University of California?

03:31:12 9 A I am.

03:31:14 10 MR. SIPES: Now, if we go to the next page, if
03:31:16 11 you could blow up --

03:31:16 12 BY MR. SIPES:

03:31:17 13 Q See the main comments from experts? Do you see that at
03:31:21 14 the top the page?

03:31:24 15 A Yes.

03:31:25 16 MR. SIPES: And then if you could blow up
03:31:27 17 just -- "the LDL-C is likely to go up."

03:31:27 18 BY MR. SIPES:

03:31:32 19 Q So the main comments from experts was,

03:31:34 20 "LDL-C is likely to go up as it does with
03:31:37 21 virtually all TG lowering therapies in this group of
03:31:42 22 patience. Note that even a low calorie diet will
03:31:44 23 raise LDL-C in these types of patients."

03:31:47 24 Do you see that?

03:31:48 25 A I see that.

03:31:49 1 Q And this is in December of 2008, correct?

03:31:51 2 A I don't know. I did not note the date on that document.

03:31:55 3 Q We can go back look at that. You would agree that 2008
03:31:58 4 is a relevant time period for this case.

03:32:01 5 A I'll also note this is an Amarin expert panel. I'm not
03:32:04 6 aware of what this physician's expertise is in terms of
03:32:09 7 preventive medicine. You've made a big deal out of me not
03:32:12 8 being a cardiologist. I don't know what his expertise is.

03:32:16 9 I think making these very broad generalizations and
03:32:20 10 these kinds of summary statements really represents their
03:32:23 11 opinion. This doesn't represent what the general consensus of
03:32:29 12 the field is or people who have an understanding of lipid
03:32:33 13 metabolism necessarily.

03:32:35 14 It certainly doesn't represent my understanding of
03:32:44 15 lipoprotein metabolism.

03:32:44 16 Q But is it your understanding that LDL-C can go up in
03:32:49 17 lowering triglycerides because of the enhanced clearance of
03:32:53 18 VLDL and IDL to LDL?

03:32:58 19 A I think there's actually multiple mechanisms that can
03:33:03 20 happen, and it depends on what the specific pathways that are
03:33:06 21 involved are and what the treatment is.

03:33:07 22 So, for example, one could imagine -- and you
03:33:10 23 remember the cascade of lipoprotein secretion where one
03:33:14 24 initial secretes a VLDL particle, and that's converted to an
03:33:20 25 IDL particles, and that's converted to an LDL particle.

03:33:23 1 So one could imagine, for example, that, yes, when
03:33:26 2 you convert VLDL to IDL and IDL to LDL you get an increase in
03:33:33 3 LDL cholesterol, yes, absolutely.

03:33:35 4 But I can also imagine if one inhibited the
03:33:38 5 synthesis of apo-B and triglyceride synthesis by the liver
03:33:41 6 that all of those lipoproteins would go down, and, in fact, I
03:33:45 7 would speculate that's the mechanism of action of EPA.

03:33:49 8 Q Let's see. But it is certainly possible that this idea
03:33:51 9 that the lipid -- the TG lowering agents including omega-3
03:33:58 10 were enhancing clearance of VLDL to LDL would explain the
03:34:06 11 general phenomenon of an increase in LDL-C in those patients,
03:34:07 12 correct?

03:34:07 13 A I would disagree with the conclusion that it's a general
03:34:11 14 mechanism.

03:34:12 15 You're taking a specific example of a drug that
03:34:15 16 elevates LDL cholesterol by the conversion of VLDL and IDL to
03:34:21 17 LDL, and, yes, I would accept that that's likely to be part of
03:34:25 18 the mechanism there.

03:34:26 19 But I believe there are other ways to lower
03:34:29 20 triglycerides that would not have that effect, and the point I
03:34:31 21 just made is, for example, if one were to inhibit the
03:34:38 22 secretion of VLDL by the liver, one would decrease VLDL and
03:34:39 23 its triglycerides, IDL and its triglycerides and cholesterol,
03:34:43 24 and IDL and its cholesterol. And, as I've just speculated,
03:34:47 25 that would be consistent with the mechanism of action of EPA.

03:34:51 1 So you're trying take one specific example of a
03:34:53 2 potential mechanism and saying that that's the only mechanism
03:34:57 3 that can result in triglyceride lowering, and I do not believe
03:35:00 4 that is correct.

03:35:02 5 MR. SIPES: Mr. Brooks, could we pull up PX 289.

03:35:07 6 THE WITNESS: I'm going to take a deep breath.

03:35:09 7 BY MR. SIPES:

03:35:09 8 Q You recognize PX 289 as the medical review, the
03:35:13 9 publically available medical review of Vascepa?

03:35:16 10 A I do not.

03:35:17 11 Q You reviewed this in your reports and cited to many
03:35:21 12 reports. Maybe in looking at it, it will refresh your
03:35:24 13 recollection. I'll tell that this is the medical review for
03:35:27 14 Vascepa.

03:35:27 15 A I'll accept that. I reviewed many, many documents for my
03:35:31 16 report.

03:35:32 17 MR. SIPES: Understandable.

03:35:33 18 And, in fact, Mr. Brooks, if you go to PX
03:35:36 19 289-0002.

03:35:36 20 BY MR. SIPES:

03:35:41 21 Q You'll see clinical review at the top.

03:35:43 22 A Yes.

03:35:44 23 Q And then the established name, icosapent ethyl, proposed
03:35:48 24 tradename Vascepa.

03:35:50 25 A Yes, I see that.

03:35:52 1 Q And it's -- the submit date for the NDA was
03:35:57 2 September 23rd, 2011. Do you see that?

03:35:59 3 A I do.

03:36:00 4 Q Okay. So --

03:36:02 5 A I'm not sure why this is relevant. I thought all the
03:36:05 6 evidence for this had to be before the filing of the patent.

03:36:09 7 Q That's an excellent point, and it's interesting that you
03:36:11 8 relied on Bays 2011 in your review of the prior art.

03:36:16 9 I'm trying to look at other contemporaneous things
03:36:16 10 to see what they're saying, but I agree with you,
03:36:21 11 Dr. Heinecke, it's very important here to focus on the prior
03:36:24 12 art.

03:36:24 13 Let's take look at page 0014, you'll see under 2.4,
03:36:31 14 Important Safety Issues With Consideration to Related Drugs.
03:36:35 15 Do you see that?

03:36:35 16 A Yes, I do.

03:36:36 17 Q And they're talking about drugs related to Vascepa, of
03:36:40 18 course, right?

03:36:41 19 A I have to read this one moment.

03:36:45 20 Q I'll direct your attention to the first paragraph that
03:36:48 21 begins,

03:36:48 22 "With regard to the only other FDA approved
03:36:52 23 omega-3 fatty acid product (Lovaza), there have been
03:36:57 24 four areas of potential safety concern: Increases in
03:37:00 25 LDL-C, liver enzymes, blood glucose, and a possible

03:37:04 1 increase in bleeding risk."

03:37:05 2 Correct?

03:37:06 3 A Yes, that's what it states.

03:37:07 4 Q And they're talking about the related omega-3 product
03:37:11 5 which contains both EPA and DHA, Lovaza, correct?

03:37:16 6 A I'm sorry, point that out to me?

03:37:18 7 Q Lovaza. You see in the very first line says Lovaza?

03:37:18 8 A Yes.

03:37:21 9 Q That was the only previously FDA approved omega-3 fatty
03:37:25 10 acid product before Vascepa, correct?

03:37:25 11 A Yes.

03:37:26 12 MR. SIPES: And then they go on to say, the next
03:37:29 13 paragraph, if you can highlight that, Mr. Brooks? Maybe blow
03:37:33 14 it up so it's easier to read?

03:37:33 15 BY MR. SIPES:

03:37:36 16 Q "The increase in LDL-C is thought to be
03:37:40 17 due to the increased activity of LPL activity."

03:37:44 18 Do you see that?

03:37:44 19 A Yes.

03:37:45 20 Q And LPL activity, of course, refers to lipoprotein
03:37:50 21 lipase, correct?

03:37:51 22 A Yes.

03:37:51 23 Q So it says,

03:37:52 24 "The increase in LDL-C is thought to be due
03:37:56 25 to the increased activity of lipoprotein lipase

activity."

(Discussion held off the record.)

MR. SIPES: So,

"The increase in LDL-C is thought to be due to the increased activity of LPL activity. This increased activity enhances the conversion of very low density lipoprotein (VLDL) and intermediate lipoproteins (IDL) to LDL-C."

Do you see that?

A I do. I note they're referring specifically to Lovaza which is a mixture of omega-3 fatty acids, and they also state "it is thought to be due," which in my mind is implying that there's some evidence that might be the case, but it's not definitively established.

Q Now --

A So they're referring to a specific mixture of omega-3 fatty acids here and a specific mechanism that might be relevant to particular intervention.

THE COURT: Dr. Heinecke, will you wait for a question before you give your answer?

THE WITNESS: I'm sorry, yes.

BY MR. SIPES:

Q So FDA, in 2011, continued to believe that the mechanism for Lovaza, the mixture of omegas-3s of EPA and DHA, was this enhanced clearance of VLDL through IDL to LDL, correct?

03:39:18 1 A Yes.

03:39:18 2 Q Now, you may recall at your deposition I asked you
03:39:21 3 whether you were aware of any particular mechanism that a
03:39:25 4 person of ordinary skill in the art in 2008 would have
03:39:28 5 attributed to EPA but not DHA. Do you recall that?

03:39:33 6 A Not specifically, but I have a feeling I'm about to find
03:39:37 7 out.

03:39:37 8 Q And you testified that you were not aware of any such
03:39:40 9 mechanism that a person of ordinary skill in the art in 2008
03:39:44 10 would have attributed to EPA but not DHA. Does that refresh
03:39:49 11 your recollection?

03:39:49 12 A What I recall is that we were -- I was deposed for eight
03:39:56 13 hours, that there was a tremendous number of different
03:39:59 14 discussions that went on, that we talked about many different
03:40:03 15 things, and that you may be taking things out of context here.

03:40:03 16 MR.

03:40:07 17 SIPES: Well, we can see. Mr. Brooks, if you
03:40:09 18 would play transcript 105 from 2 to 7.

03:40:15 19 (Deposition video recording played.)

03:40:36 20 MR. SIPES: All right, Mr. Brooks.

03:40:36 21 BY MR. SIPES:

03:40:38 22 Q Do you recall giving that answer?

03:40:39 23 A Can we go back to exactly what I said, please?

03:40:44 24 MR. SIPES: Mr. Brooks, could you play it again?

03:40:45 25 THE WITNESS: No, no, just give me the -- can

03:40:47 1 you give me the print instead of a video?

03:41:02 2 MR. SIPES: May I approach?

03:41:03 3 THE COURT: Yes.

03:41:06 4 THE WITNESS: How do I find it?

03:41:10 5 MR. SIPES: It's at page 105.

03:41:19 6 THE COURT: It's also on the monitor for you,
03:41:21 7 Doctor.

03:41:22 8 THE WITNESS: Okay. That's better. That's
03:41:24 9 fine. Thank you.

03:41:33 10 I guess I said what I said.

03:41:35 11 "Is there a particular mechanism that a
03:41:38 12 person of ordinary skill in the art in 2008 would
03:41:42 13 have attributed to EPA, but not DHA?"

03:41:46 14 Since we don't know what the mechanism is for
03:41:49 15 either drug, in my opinion, I would say that that's a fair
03:41:54 16 statement, and --

03:42:00 17 MR. SIPES: All right. Let me --

03:42:02 18 THE WITNESS: In my opinion, we don't know how
03:42:04 19 EPA or DHA are working.

03:42:07 20 I don't think that trying to describe specific
03:42:10 21 mechanisms when we don't know what the mechanism is, is
03:42:14 22 obviously difficult.

03:42:15 23 And, moreover, I would also state that they may
03:42:18 24 share mechanisms, and they may have distinct mechanisms. And,
03:42:23 25 in fact, from the differential effects of the two drugs on LDL

1 cholesterol, I would suspect very strongly they have different
2 mechanisms of action.

3 And I also believe that earlier in the
4 discussion we did talk about potential mechanisms, and one of
5 the things that I alluded to is the fact that people have
6 speculated or proposed that, for example, EPA and DHA are
7 substrates for a family of enzymes that converts them into
8 bioactive mediators, and there's been some thought that EPA
9 and DHA yield, by that pathway, molecules that are derived
10 from them but have this very different biological effects.

11 MR. SIPES: So I think you mentioned that you
12 were concerned about the medical review, that it was even
13 after 2008, and they were taking this view.

14 Let's take a look at PX 923.

15 PX 923 -- and if you go -- it's easier to see if
16 you go to the next page. Mr. Brooks, the third page. I
17 apologize.

18 BY MR. SIPES:

19 Q It's an article in the *American Journal of the Health*
20 *System Pharmacy* entitled "Prescription Omega-3 Fatty Acids For
21 the Treatment of Hypertriglyceridemia," by James McKenney and
22 Dominic Sica. Do you see that?

23 A Yes, I do.

24 Q And you would you agree that Plaintiffs' Exhibit 923
25 is -- is literature that was published before 2008, correct?

03:43:53 1 A Yes.

03:43:55 2 MR. SIPES: Your Honor, I'd move PX 923 into
03:43:57 3 evidence.

03:43:58 4 MR. REIG-PLESSIS: No objection.

03:43:58 5 THE COURT: 923 is admitted.

03:43:58 6 (Plaintiffs' Exhibit 923 received in
03:43:58 7 evidence.)

03:44:02 7 MR. SIPES: Mr. Brooks, if you'll turn to
03:44:04 8 page 0005, and blow up the right-hand column beginning with
03:44:16 9 "importantly."

03:44:16 10 BY MR. SIPES:

03:44:18 11 Q So here, too, the authors are suggesting how
03:44:24 12 prescription omega-3 fatty acids work, correct?

03:44:28 13 A I need a moment to read this.

03:44:30 14 Q Well, if you -- let me read it to you.

03:44:32 15 A All right.

03:44:33 16 Q It says,

03:44:33 17 "Importantly, the conversion of VLDL to LDL
03:44:37 18 particles increased 93 percent on the influence of
03:44:41 19 prescription omega-3 fatty acids. These results
03:44:45 20 illustrate that the enhanced catabolism of
03:44:49 21 triglycerides produced by prescription omega-3 fatty
03:44:52 22 acids results in less secretion and more rapid
03:44:54 23 removal of VLDL particles. The results also show
03:44:58 24 that VLDL particles are rapidly converted to LDL
03:45:03 25 particles, thus explaining why LDL cholesterol levels

03:45:07 1 may rise in patients with very high triglycerides
03:45:09 2 when given prescription omega-3 fatty acid therapy."

03:45:16 3 Did I read that correctly, Dr. Heinecke?

03:45:18 4 A Yes, you did.

03:45:19 5 Q It's fair to say we've now looked all the way in 2007
03:45:23 6 back in '77, in 2011.

03:45:25 7 There was a consistent theme here that people with
03:45:28 8 severe hypertriglyceridemia are particularly subject to rises
03:45:30 9 in LDL-C when their triglycerides are lowered because of the
03:45:35 10 conversion of VLDL through IDL to LDL, correct?

03:45:42 11 A My interpretation of what you're saying is that you're
03:45:46 12 picking out articles that support your point of view and
03:45:49 13 citing them.

03:45:50 14 I don't know whether or not, for example, this is
03:45:52 15 true, that VLDL is converted to LDL particles by 93 percent
03:45:57 16 under the influence of fish oil.

03:45:59 17 So I think -- again, you're making very broad
03:46:02 18 conclusions without -- I mean, I haven't read the particular
03:46:07 19 literature they're citing here so I can't comment on it, but I
03:46:11 20 feel like you're making very broad generalizations from very
03:46:15 21 specific examples where you're allowed to pick out the
03:46:18 22 specific references you want without any context of what the
03:46:21 23 overall literature is or what other people might be thinking
03:46:25 24 about the mechanisms are.

03:46:27 25 Q Dr. Heinecke, are you seriously -- having gone through a

03:46:31 1 selection of the prior art in the last couple hours --
03:46:33 2 complaining that there's additional art that doesn't support
03:46:36 3 your opinion?

03:46:37 4 A I'm sorry, state that again?

03:46:40 5 Q That's all right. I'll withdraw the question.

03:46:41 6 Let me ask you, I think you've distinguished the
03:46:45 7 omega-3s from Tricor by suggesting that fibrates are PPAR
03:46:51 8 inhibitors?

03:46:53 9 A I said there was evidence from animal studies that they
03:46:56 10 might act via the PPAR activators, but I also stated, I
03:47:02 11 believe, that the evidence that that's relevant to human
03:47:06 12 biology is not very convincing and that many other mechanisms
03:47:10 13 have been proposed as well.

03:47:11 14 MR. SIPES: Mr. Brooks, if you can pull up --

03:47:13 15 THE WITNESS: And I have --

03:47:14 16 MR. SIPES: Blow up the bottom of the middle
03:47:16 17 paragraph in the McKenney article that begins "second omega
03:47:22 18 fatty acids." It's at the bottom of the middle column. Blow
03:47:26 19 up the second -- right there. If you could blow it up, it's
03:47:29 20 hard to read the way it is.

03:47:29 21 BY MR. SIPES:

03:47:34 22 Q McKenney reports,

03:47:35 23 "Second, omega-3 fatty acids appear to induce
03:47:41 24 peroxisomal B-oxidation in the liver. Hepatic
03:47:41 25 nuclear receptors, such as peroxisome proliferator-

03:47:50 1 activated receptors (PPARs), are thought to mediate
03:47:53 2 the hypolipidemic effect of polyunsaturated fatty
03:47:58 3 acids."

03:47:58 4 Do you see that?

03:47:59 5 A I do.

03:48:00 6 Q There's a suggestion that omega-3 fatty acids are also
03:48:05 7 PPAR inhibitors, correct?

03:48:05 8 A There's a suggestion, that's correct. That's one
03:48:08 9 proposed mechanism.

03:48:10 10 As I alluded to earlier, that's based on studies, in
03:48:13 11 my opinion, using knock-out mice where they have a specific
03:48:18 12 deficiency in this receptor, and then they can implicate
03:48:22 13 directly changes in biological effects to the presence or
03:48:26 14 absence of the receptor.

03:48:28 15 The relevance of those studies to humans is
03:48:32 16 completely unknown. Mice and humans have completely different
03:48:35 17 lipid metabolism. For example, mice have extremely high
03:48:40 18 levels of HDL cholesterol and very low levels of LDL
03:48:42 19 cholesterol in marked distinction to what humans have. They
03:48:45 20 lack enzymes that play critical roles in lipoprotein
03:48:45 21 metabolism in humans.

03:48:48 22 So I think making these kinds of studies --
03:48:51 23 conclusions on these kinds of studies is not relevant to human
03:48:55 24 biology.

03:48:56 25 Q It's extremely difficult, is it not, to predict the

03:48:59 1 clinical effects of a drug without testing it in humans.

03:49:03 2 A I would agree with that fully.

03:49:05 3 MR. SIPES: Mr. Brooks, if you would pull up the
03:49:07 4 bottom of the left-hand column through the middle of the top
03:49:12 5 paragraph of the middle column.

03:49:15 6 So the very bottom of the (unintelligible)
03:49:18 7 beginning "the triglycerides reducing effects." If you could
03:49:20 8 pull that up, and then in the middle column -- no the middle
03:49:24 9 column on that same page.

03:49:28 10 All right. I don't know if it's -- I'm hoping
03:49:30 11 it's readable. I'm trying to make it readable. Maybe --
03:49:32 12 there we go. If you could pull it down so we can see it from
03:49:36 13 the top.

03:49:37 14 Okay. I'll try to read it to you.

03:49:40 15 The article also says,

03:49:42 16 "The triglyceride-reducing effects of EPA and
03:49:45 17 DHA have been detailed in numerous studies among a
03:49:49 18 wide range of patient types. A dose response
03:49:51 19 relationship between EPA or DHA and triglyceride
03:49:55 20 lowering has been demonstrated with doses between 2
03:49:58 21 and 4 grams per day lowering serum triglycerides by
03:50:01 22 approximately 20 and 50 percent. As with fibric acid
03:50:09 23 derivatives (fibrates) and nicotinic acid (niacin),
03:50:09 24 reductions in triglycerides and
03:50:12 25 very-low-density-lipoprotein (VLDL) cholesterol are

generally greater in patients with higher baseline triglyceride levels. An increase in low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol can accompany a reduction in triglycerides; the higher the baseline triglyceride level, the greater these lipids may be increased."

BY MR. SIPES:

Q Did I read that correctly, Dr. Heinecke?

A Yes, it says "can accompany a reduction in triglycerides."

Q And it's fair to say that in the McKenney article, the omega-3 fatty acids, EPA, VHA, niacin, and fibrates, are all lumped together as lowering triglycerides and raising LDL, correct?

A Again, I think you're way -- I think you're over generalizing here. You're ignoring the fact that statins, for example, will very potently lower triglycerides and LDL cholesterol in patients as well, and this is clearly not consistent with your idea that these are all acting by the same mechanism and have the same deleterious effects.

So I think you're just making very broad conclusions based on selective citation of the literature.

I don't -- and I'll just also add you're throwing an awful lot of information at me here and asking me to digest

03:51:27 1 it. I don't have a chance to look at the specific references.
03:51:29 2 I don't know where these studies were carried out. So I think
03:51:33 3 is very difficult for me to evaluate on the front of it.

03:51:36 4 But if you're asking me do all drugs that lower
03:51:39 5 triglycerides raise LDL, no, I don't agree with that, and I
03:51:43 6 think the example of statins is a perfectly congruent one.

03:51:47 7 Q Of course, a classic example now, in this case, is
03:51:51 8 Vascepa.

03:51:52 9 A I'm sorry, restate the question again. Was there a
03:51:55 10 question?

03:51:56 11 Q You said -- you asked me a question is there an example
03:51:58 12 of a drug that lowers triglycerides without raising LDL-C in
03:52:02 13 very high triglyceride patients. An example of that is
03:52:07 14 Vascepa, correct?

03:52:07 15 A That would argue against what you're saying, I think.

03:52:10 16 I mean, you can't have it both ways. You can't say
03:52:12 17 that all drugs that lower triglycerides elevate LDL except for
03:52:18 18 Vascepa when there's another example which is statins. It
03:52:21 19 seems to me you're arguing against your own conclusion.

03:52:25 20 MR. SIPES: Mr. Brooks, let's go back and look
03:52:27 21 at the concern here. Let's go back to Carlson's 1977 PX 1026.
03:52:36 22 If we go to page 0007. Blow up the middle paragraph.

03:52:36 23 BY MR. SIPES:

03:52:49 24 Q The authors conclude in their report -- you recall this
03:52:52 25 is the report on the rise in LDL-C in treating very high

triglycerides with niacin.

"The finding of major clinical concern," and that's emphasized, "in this report is the sometimes quite substantial rise in LDL cholesterol. This may be quite atherogenic and theoretically the benefit of lowering VLDL in these patients may be overridden by the potential danger due to the rise in LDL."

Did I read that correctly, Dr. Heinecke?

A You're reading the authors' conclusion, not mine.

Q The authors are expressing a major clinical concern about the rise in LDL-C in patients with severe hypertriglyceridemia, correct?

A As we noted before, this was study in four patients, and, as I also alluded to earlier, I couldn't actually find what the levels of triglycerides were in this study.

Q Dr. Heinecke, your counsel will have an opportunity to draw out additional testimony on redirect. I would appreciate it if you could answer my questions, or we will be here for days.

A I agree this is what the authors are stating. That doesn't necessarily mean that I agree with the conclusion.

Q Let's take a look, if you will, at Tricor to see what Tricor does. Let's look at PX 388.

PX PX388, do you recognize this as the 2004 approved labeling for Tricor? And I can guide you through that if it

03:54:26 1 would help you.

03:54:27 2 A I don't recognize it, but I accept that that's correct.

03:54:30 3 MR. SIPES: If you go to the second page,

03:54:32 4 Mr. Brooks.

03:54:33 5 BY MR. SIPES:

03:54:33 6 Q You'll see that on the top it says Tricor?

03:54:36 7 A Yes.

03:54:37 8 Q Fenofibrate tablets.

03:54:40 9 And if we go to the last page --

03:54:41 10 A Can we just remain there for a moment?

03:54:43 11 I'll just point out that the chemical structure of
03:54:46 12 Tricor is shown there, and it bears no structural resemblance
03:54:49 13 to omega-3 fatty acids.

03:54:49 14 Q Dr. Heinecke, you will have opportunity with your
03:54:52 15 counsel. We need to move through this, or it will go on
03:54:55 16 forever.

03:54:56 17 A I'm with you on this. Let's get it done.

03:54:59 18 Q So if we go to PX388 at 0018. The date of approval here
03:55:13 19 is shown as November 5, 2004, correct?

03:55:17 20 A Yes.

03:55:18 21 MR. SIPES: So, Your Honor, I would move PX388
03:55:22 22 into evidence.

03:55:22 23 MR. REIG-PLESSIS: No objection.

03:55:23 24 THE COURT: 388 is admitted.

03:55:23 25

(Plaintiffs' Exhibit 388 received in evidence.)

MR. SIPES: First, if we look at, Mr. Brooks, PX

PX388 on page 0006.

BY MR. SIPES:

Q In the Pooled Cohort, that's the top box there, Dr. Heinecke, you'll see that the patients with a mean TG level of 191 milligrams per deciliter, correct?

A I'm sorry. Can you state that again?

Q Yes, the study reported in Table 1 under Pooled Cohort --

A Yes.

Q -- shows patients with triglyceride levels, mean baseline triglycerides levels, of 191 milligrams per deciliter.

A Yes.

Q And those patients were administered Fenofibrate, correct?

A Yes.

Q And their LDL-C went down 20.6 percent, correct?

A Yes.

Q And that was a statistically significant result, correct?

A I assume that's what the star means, so yes.

Q Yes. And then the subgroup, whose triglycerides were 231.9 milligrams per deciliter, do you see that?

A Yes.

Q Their LDL-C went down with Fenofibrate 20.1 percent.

A Yes.

03:56:56 1 Q So these -- this is an example of a TG lowering agent
03:56:59 2 that reduced triglycerides in patients with elevated but not
03:57:03 3 very high triglycerides in which -- it reduced triglycerides
03:57:08 4 and reduced LDL-C, correct?

03:57:10 5 A Yes.

03:57:10 6 Q But, of course, if we look at Table 2, Study 2 reports
03:57:22 7 study on patients with a baseline TG between 500 and
03:57:27 8 1500 milligrams per deciliter, correct?

03:57:29 9 A I'm sorry. I can't see that. Could you point that ought
03:57:32 10 for me, please?

03:57:33 11 Q You see Table 2, there's Study 1 and Study 2?

03:57:36 12 A Yes.

03:57:37 13 Q Study 1 is a baseline TG between 350 and 499.

03:57:44 14 A Yes.

03:57:45 15 Q And Study 2 is a baseline triglyceride level between 500
03:57:49 16 and 1500, correct?

03:57:50 17 A Yes.

03:57:51 18 Q So Study 1 is what we call high triglycerides, correct?

03:57:56 19 A Correct.

03:57:57 20 Q Study 2 is very high triglycerides, correct?

03:58:00 21 A Correct.

03:58:00 22 Q Let's first look at the very high triglyceride patients.
03:58:04 23 Their LDL cholesterol went up a placebo adjusted 49.2 percent,
03:58:11 24 correct?

03:58:12 25 A Could you highlight that for me, please?

03:58:14 1 MR. SIPES: That would be -- Mr. Brooks, it's
03:58:17 2 the bottom study, LDL cholesterol, all the way across.

03:58:17 3 BY MR. SIPES:

03:58:23 4 Q Do you see that?

03:58:24 5 A Yes, I see that.

03:58:25 6 Q So for very high triglyceride patients receiving
03:58:28 7 Fenofibrate to reduce triglycerides, their LDL-C went up
03:58:33 8 49.2 percent.

03:58:34 9 A Patients in this particular study treated with this
03:58:41 10 particular agent, that's correct.

03:58:43 11 Q And that was, of course, statistically significant,
03:58:48 12 correct?

03:58:48 13 A I would assume so, yes.

03:58:50 14 Q It's got the asterisk which you'll see means P value
03:58:54 15 below .05. Do you see that, Dr. Heinecke?

03:58:58 16 A Yeah, I accept that it's correct.

03:59:00 17 MR. SIPES: Now, let's look at the high
18 triglyceride patients between 350 and 499 cholesterol.

19 Mr. Brooks, could you highlight the
20 cholesterol -- the LDL cholesterol there.

21 BY MR. SIPES:

22 Q There the LDL cholesterol went up from administering
03:59:17 23 Tricor numerically 2.5 percent relative to placebo.

03:59:21 24 A Okay.

03:59:22 25 Q And it was not statistically significant, correct?

03:59:26 1 A Correct.

03:59:27 2 Q Which I think in the parlance you used earlier today, you
03:59:31 3 would say Fenofibrate was LDL neutral in high triglyceride
03:59:37 4 patients is the way you referred to that kind of change,
03:59:41 5 correct?

03:59:42 6 A I don't believe I used the term LDL neutral. But I would
03:59:46 7 agree that the LDL cholesterol did not change significantly in
03:59:50 8 this particular study.

03:59:51 9 Q In fact, I think in referring to Mori, which went up --
03:59:55 10 EPA increased LDL cholesterol 3.5 percent, but not
04:00:00 11 statistically significant, 3.5 percent, you said that was
04:00:05 12 LDL -- or maybe you said LDL-C neutral. Does that sound
04:00:07 13 familiar to you?

04:00:07 14 A I said that it did not increase significantly, I believe.

04:00:12 15 Q So, in fact -- and that was in a -- the Mori patient
04:00:18 16 population was a dyslipidemia patient with lower
04:00:22 17 triglycerides, more like Study 1 -- Table 1, in Tricor,
04:00:25 18 correct? With even lower triglycerides than we have with
04:00:28 19 Fenofibrate.

04:00:30 20 A I'm not understanding this line of questioning.

04:00:33 21 Q So let me just ask this as a factual question. In Mori,
04:00:36 22 the triglycerides were under 200, correct?

04:00:40 23 A Yes.

04:00:40 24 Q Okay. So -- they were not even the high triglycerides --
04:00:47 25 they didn't even have high triglycerides, correct?

04:00:48 1 A Yes.

04:00:48 2 Q But what we're seeing from Tricor is that these very high
04:00:56 3 triglyceride patients are uniquely susceptible to an increase
04:01:00 4 in LDL-C in reducing triglycerides even in agents that don't
04:01:04 5 raise LDL-C in other patients, correct?

04:01:08 6 A Again, I think you're generalizing from a very specific
04:01:12 7 example to all drugs and how they act, and, in my opinion,
04:01:17 8 that's not a correct way to think about the problem.

04:01:19 9 It's clear that fibric acids are different from
04:01:23 10 statins, are different from EPA, are different from DHA, and
04:01:28 11 trying to take one drug under one specific set of conditions
04:01:31 12 and saying that indicates what the general mechanism is that's
04:01:35 13 always going to take place, that's just -- to me is not -- not
04:01:40 14 the correct way to think about the problem.

04:01:42 15 Q There's a great deal of unpredictability in moving it to
04:01:45 16 a new patient population, correct?

04:01:47 17 A Well, that's a very broad statement. I don't know what
04:01:51 18 you mean by that.

04:01:52 19 MR. SIPES: Okay. Let's take a look the
04:01:54 20 clinical pharmacology section of Tricor just to understand
04:01:57 21 what we're talking about here.

04:01:58 22 Mr. Brooks, if you'll turn first to PX 388-02.
04:01:58 23 BY MR. SIPES:

04:02:07 24 Q If you go down, you'll see there's a section Clinical
04:02:10 25 Pharmacology. Do you see that, Dr. Heinecke?

04:02:11 1 A Yes, I do.

04:02:12 2 MR. SIPES: Okay. And if we turn to the next
04:02:13 3 page, and if you could blow up the paragraph that begins, "The
04:02:17 4 effects of fenofibric acid."

04:02:17 5 BY MR. SIPES:

04:02:18 6 Q So, Dr. Heinecke, it reads,

04:02:24 7 "The effects of fenofibric acid seen in
04:02:24 8 clinical practice have been explained *in vivo* in
04:02:24 9 transgenic mice and *in vitro* in human hepatocyte
04:02:24 10 cultures by the activation of peroxisome proliferator
04:02:24 11 activated receptor alpha (PPAR Alpha)."

04:02:32 12 Boy, I hope I never have to read that again.

04:02:45 13 "Through this mechanism, fenofibrate
04:02:45 14 increases lipolysis and elimination of
04:02:53 15 triglyceride-rich particles from plasma by activating
04:02:53 16 lipoprotein lipase and reducing production of
04:02:53 17 apoprotein C-III (an inhibitor of lipoprotein lipase
04:02:53 18 activity)."

04:02:53 19 Do you see that?

04:03:05 20 A I'll point out that they're talking about *in vivo* studies
04:03:09 21 in transgenic mice which, as I've already alluded to, I do not
04:03:13 22 believe is an appropriate model for human lipoprotein
04:03:13 23 metabolism.

04:03:14 24 And, moreover, they're citing tissue culture studies
04:03:21 25 of human hepatocytes which are even more dubious. So I'm not

04:03:22 1 clear why they're concluding that this indicates this is the
04:03:23 2 mechanism of action in humans in vivo.

04:03:27 3 Q You understand, of course -- I just asked a simple
04:03:30 4 question. What we're talking about here is the FDA-approved
04:03:33 5 labeling for Tricor, correct?

04:03:35 6 That's a yes or no question, Dr. Heinecke.

04:03:37 7 A Yeah, I can't -- I can't honestly attest to that, but
04:03:41 8 I'll accept it's correct.

04:03:42 9 Q And the mechanism for fenofibrate to lower triglycerides
04:03:46 10 that is being suggested in the FDA-approved labeling in 2004
04:03:50 11 is the enhanced clearance of VLDL to LDL-C, correct?

04:03:56 12 A I think this is what the FDA is stating here, but I'm
04:03:59 13 clearly indicating that I think that's an incorrect
04:04:02 14 conclusion, and I would never agree with this assessment.

04:04:05 15 And there's nothing magical about the FDA and their
04:04:09 16 reasoning. They can make mistakes. This is clearly -- I
04:04:13 17 mean, really, you're telling me that transgenic mice lacking
04:04:17 18 PPAR Alpha, which is a pleiotrophic nuclear receptor that has
04:04:23 19 innumerable effects, not just this, in both humans and in
04:04:25 20 animals, is somehow telling us what the mechanism is, and they
04:04:29 21 buttress that by studying cultured tissue cells?

04:04:31 22 No, I would not -- I just wouldn't agree with this,
04:04:33 23 I'm sorry.

04:04:34 24 Q Dr. Heinecke, in 2000, you --

04:04:36 25 A This might be the FDA's conclusion, but it's not my

04:04:40 1 conclusion.

04:04:40 2 THE COURT: So, Dr. Heinecke --

04:04:41 3 THE WITNESS: Yes.

04:04:42 4 THE COURT: You should listen to the question
04:04:44 5 asked. There was no question asked whether you agree with the
04:04:47 6 FDA or your opinion of the FDA.

04:04:49 7 You should take your advice about breathing
04:04:52 8 before you answer.

04:04:52 9 THE WITNESS: Thank you.

04:04:53 10 THE COURT: So let's wait for the question.

04:04:53 11 THE WITNESS: Thank you.

04:04:53 12 THE COURT: All right?

04:04:55 13 THE WITNESS: Thank you. I will try and do
04:04:56 14 that. Thank you very much, Your Honor.

04:04:58 15 BY MR. SIPES:

04:04:59 16 Q Dr. Heinecke, in 2000, you won the Simon Wolff Contrarian
04:04:59 17 Award, correct?

04:05:07 18 A That's correct.

04:05:07 19 Q Okay.

04:05:08 20 A One of many awards I've won.

04:05:10 21 Q You've been recognized as a contrarian.

04:05:14 22 A Let me -- can I just --

04:05:16 23 Q It's a yes or no question, Doctor. You can explain with
04:05:19 24 your counsel.

04:05:19 25 A Yes. Yes.

04:05:20 1 Q Thank you.

04:05:22 2 If we could pull up PX 1027. This is *Goodman &*
04:05:28 3 *Gilman's The Pharmacological Basis of Therapeutics, Eleventh*
04:05:33 4 *Edition*. Do you see that?

04:05:33 5 A Yes, I do.

04:05:35 6 Q And Goodman & Gilman's is very well-known reference for
04:05:38 7 pharmacology and therapeutics, correct?

04:05:40 8 A Yes.

04:05:41 9 Q And the eleventh edition is from 2006, correct?

04:05:44 10 A Yes.

04:05:45 11 MR. SIPES: We would move --

04:05:45 12 THE WITNESS: I don't know that, but I'll accept
04:05:47 13 that it's correct.

04:05:48 14 MR. SIPES: I can clarify it if you would like
04:05:48 15 because --

04:05:50 16 THE WITNESS: No, I believe you.

04:05:51 17 MR. SIPES: Okay. I will move PX 1027 into the
04:05:54 18 record -- move 1027 into evidence, if I can.

04:05:59 19 MR. REIG-PLESSIS: No objection.

04:06:00 20 THE COURT: Is there objection?

04:06:01 21 All right, 1027 is admitted.

04:06:01 22 (Plaintiffs' Exhibit 1027 received in
04:06:01 evidence.)

04:06:06 23 MR. SIPES: So, Mr. Brooks, if you will turn to
04:06:18 24 page 1027-0030.

04:06:18 25

04:06:18 1 BY MR. SIPES:

04:06:20 2 Q The topic refers to fibric acid derivatives. Do you see
04:06:20 3 that?

04:06:28 4 A I do.

04:06:28 5 Q And that would include fenofibrate and the other
04:06:33 6 fibrates, correct?

04:06:33 7 A Yes.

04:06:33 8 Q And then the bottom paragraph has mechanism action. Do
04:06:39 9 you see that?

04:06:40 10 A Yes.

04:06:40 11 Q And here again --

04:06:41 12 MR. SIPES: Mr. Brooks, if would you pull up the
04:06:42 13 sentence that begins "fibrates reduce," and go up through to
04:06:48 14 the end. Thank you.

04:06:51 15 "Fibrates reduce triglycerides through
04:06:54 16 PPAR-alpha-mediated stimulation of fatty acid
04:06:59 17 oxidation, increased LPL synthesis, and reduced
04:07:02 18 expression of apoC-III. An increase in LPL would
04:07:07 19 enhance the clearance of triglyceride-rich
04:07:10 20 lipoproteins."

04:07:11 21 Do you see that?

04:07:12 22 A That's what's stated there.

04:07:13 23 Q So Goodman & Gilman's as well is reporting this idea that
04:07:17 24 fibrates work by enhancing the clearance of VLDL through to
04:07:23 25 LDL, correct?

04:07:23 1 A Might we go back to the top of the paragraph there,
04:07:28 2 Mechanism of Action, which states,

04:07:30 3 "Despite extensive studies in humans, the
04:07:30 4 mechanisms by which fibrates lower lipoprotein
04:07:30 5 levels, or raise HDL levels, remains unclear."

04:07:30 6 Q What is being suggested in Goodman & Gilman's is that
04:07:30 7 fibrates work by enhancing the clearance of VLDL through IDL
04:07:46 8 to LDL, correct?

04:07:46 9 A They're suggesting that that's one potential mechanism,
04:07:50 10 yes.

04:07:50 11 MR. SIPES: Now, if we go to the next page,
04:07:53 12 Mr. Brooks, and blow up the second full paragraph.

04:07:53 13 BY MR. SIPES:

04:08:01 14 Q Here Goodman & Gilman is talking about the use of
04:08:04 15 fibrates to treat hypertriglyceridemia, correct?

04:08:06 16 A I'll need a minute to read this.

04:08:09 17 Q I'll read it to you.

04:08:09 18 A Okay.

04:08:09 19 Q Okay.

04:08:11 20 "In patients with mild hypertriglyceridemia
04:08:14 21 (e.g., triglycerides below 400 milligrams per
04:08:18 22 deciliter), fibrate treatment increases triglyceride
04:08:21 23 levels by up to 50 percent" --

04:08:22 24 THE COURT: I think it says decreases.

04:08:24 25 MR. SIPES: Decreases, I'm sorry.

"...decreases triglyceride levels by up to 50 percent and increases HDL-C concentrations about 15 percent; LDL-C levels may be unchanged or increase. The second-generation agents such as fenofibrate, bezafibrate, and ciprofibrate, lower VLDL levels to a degree similar to that produced by gemfibrozil, but they also are more likely to decrease LDL levels by 15 percent to 20 percent. In patients with more marked hypertriglyceridemia, for example 400 to 1000 milligrams per deciliter, a similar fall in triglycerides occurs, but LDL increases of 10 percent to 30 percent are seen frequently."

Did I read that correctly?

A Yes, except for the increase-decrease part.

Q And then it goes on to say,

"Normohypertriglyceridemic patients with heterozygous familial hypercholesterolemia usually experience little change in LDL levels with gemfibrozil; with the other fibric acid agents, reductions as great as 20 percent may occur in some patients."

Did I read that correctly, Dr. Heinecke?

A Yes.

Q So Goodman & Gilman, too, is informing a person of

04:09:38 1 ordinary skill in the art that patients with severe
04:09:45 2 hypertriglyceridemia may be subject to dramatic increases in
04:09:48 3 LDL-C even with agents that lower LDL-C in other patients,
04:09:53 4 correct?

04:09:53 5 A I believe they're referring specifically to the fibric
04:09:56 6 acids here.

04:10:29 7 Q Let's look at Hayashi. Hayashi is the one reference
04:10:41 8 among your key prior art that you said -- Dr. Heinecke, do you
04:10:44 9 need to take a break?

04:10:46 10 A Let's keep moving on.

04:10:48 11 Q Okay.

04:10:48 12 THE COURT: If you want to take a break, we can
04:10:50 13 take a break.

04:10:51 14 MR. SIPES: Actually, a five-minute bio-break
04:10:54 15 actually would be appreciated.

04:10:56 16 THE COURT: We'll take a break.

04:10:58 17 (A recess was taken.)
04:10:58 18

04:22:49 18 THE COURT: Please be seated.
04:22:52 19 Are you ready to resume?

04:22:54 20 MR. SIPES: I'm ready to resume.

04:22:55 21 THE COURT: All right.

04:22:56 22 MR. SIPES: Thank you, Your Honor.

04:22:58 23 THE COURT: All right.

04:22:59 24 MR. SIPES: Mr. Brooks, if we could pull up DDX
04:23:02 25 6.46.

04:23:07 1 Dr. Heinecke, do you recognize DDX 6.46? It's a
04:23:13 2 timeline that you put together that shows a number of the
04:23:16 3 prior art that you're relying on in this case?

04:23:18 4 A Yes, I recognize it.

04:23:19 5 Q And you'll see this is the timeline as 2001, correct?

04:23:25 6 A Yes.

04:23:25 7 Q It's got ATP III on it, it's got Mori on it, Kurabayashi,
04:23:29 8 Harris, Hayashi, Takaku, the Epadel label, correct?

04:23:38 9 A Yes.

04:23:38 10 Q And so that's spanning more that a decade of studies on
04:23:43 11 EPA, correct?

04:23:43 12 A Yes.

04:23:44 13 Q And the very next thing that happens is, in 2004, Reliant
04:23:47 14 and GSK developed Lovaza for the treatment of severe
04:23:52 15 hypertriglyceridemia, correct?

04:23:53 16 A Yes.

04:23:53 17 Q Neither Reliant or GSK used EPA, pure EPA, to treat
04:24:03 18 hypertriglyceridemia, correct?

04:24:04 19 A Yes, correct.

04:24:07 20 Q Okay. And so, in fact, a lot of time passed between pure
04:24:13 21 EPA and Epadel in 1991, and the invention here in 2008, of
04:24:19 22 using pure EPA to treat severe hypertriglyceridemia, correct?
04:24:21 23 That's just a lot of time.

04:24:23 24 A I believe it's true that it's been -- it's true that it
04:24:33 25 was a long time before EPA was developed as a drug to treat

04:24:40 1 hypertriglyceridemia, that's correct.

04:24:42 2 Q Now, one thing you don't have on your timeline is all of
04:24:45 3 the clinical studies that Amarin and its predecessor, Laxdale,
04:24:51 4 were doing during that time period, correct? They're not on
04:24:56 5 your timeline.

04:24:56 6 A Right. They were after 2008.

04:24:58 7 Q Is it your testimony that the CNS indications were after
04:25:04 8 2008? Is that your understanding?

04:25:06 9 A I don't have an understanding of when those studies were
04:25:10 10 carried out.

04:25:10 11 Q Okay. So it's possible, in fact, that the Huntington's,
04:25:13 12 the schizophrenia, the depression, all the Phase I studies on
04:25:17 13 Vascepa were done before 2008, correct?

04:25:19 14 A Yes.

04:25:19 15 Q But they're not on your timeline, correct?

04:25:23 16 A Yes.

04:25:24 17 Q And, in fact, just so you're aware of them, if we'll go
04:25:28 18 to PX 289, this is the Vascepa medical review. So this is
04:25:32 19 reviewing the clinical studies that were submitted to support
04:25:36 20 the MARINE indication, correct?

04:25:38 21 A I'll take your word for it.

04:25:39 22 Q Okay. So if we go to page 289-0072, it says "Review of
04:25:48 23 Safety." Do you see that?

04:25:50 24 A Yes.

04:25:51 25 Q And it refers to the clinical studies that were submitted

04:25:56 1 by Amarin in support of the MARINE indication, correct?

04:26:01 2 A I'll take your word for it.

04:26:04 3 Q Okay. Well, I'll read it to you.

04:26:06 4 First there's, "The healthy subjects dataset
04:26:09 5 included two clinical pharmacology studies,
04:26:12 6 LA01.01.0009 and AMR-01.01.0018?"

04:26:15 7 Do you see that?

04:26:17 8 A Yes, I do.

04:26:17 9 Q Okay. So that's a Laxdale study and an Amarin study,
04:26:21 10 correct?

04:26:22 11 A I'll take your word for it.

04:26:24 12 Q Okay. And then there's the hypertriglyceridemic
04:26:28 13 placebo-controlled dataset of MARINE and ANCHOR.

04:26:31 14 Do you see that?

04:26:31 15 A Yes.

04:26:32 16 Q And then there's,

04:26:32 17 "The CNS placebo-controlled dataset included
04:26:36 18 information from the double-blind phases of the eight
04:26:39 19 trials of patients with CNS disorders. There were
04:26:42 20 approximately 700 patients on Vascepa and 519
04:26:45 21 patients on placebo in this dataset," correct?

04:26:48 22 A Yes.

04:26:48 23 Q None of that is in your timeline, correct?

04:26:52 24 A Yes.

04:26:52 25 Q Okay. Let's go to Hayashi. That's DX 1532.

04:26:59 1 So I think you were testifying -- you testified
04:27:04 2 about Hayashi and whether or not there were patients in
04:27:08 3 Hayashi that were over 500.

04:27:10 4 A Yes.

04:27:11 5 MR. SIPES: And I think you pointed to the Table
04:27:15 6 1 which has the distribution of patients.

04:27:18 7 If we could pull that up, Mr. Brooks. That's
04:27:21 8 on -- I wish I knew what page it's on. It's on page 26 of the
04:27:24 9 article. This is DX 1532.

04:27:28 10 Unfortunately, I don't know what the exhibit
04:27:30 11 page number is, but it's 26 of the article --

04:27:35 12 COMPUTER TECHNICIAN: Five.

04:27:35 13 MR. SIPES: Five? Five. Thank you, Mr. Brooks.
04:27:35 14 BY MR. SIPES:

04:27:37 15 Q And you pointed there, for triglyceride levels, it was
04:27:39 16 300 plus or minus 233, correct?

04:27:42 17 A Yes.

04:27:42 18 Q And you speculated there could be four or five patients
04:27:46 19 over 500.

04:27:47 20 A Yes, based on my understanding of the standard deviation
04:27:50 21 in those values.

04:27:51 22 Q Now, of course, it's plus or minus. There could be very
04:27:55 23 low TG patients instead to get that distribution, correct?

04:27:57 24 A That's possible, although triglycerides are usually
04:28:01 25 skewed towards higher values. But, that's correct.

04:28:03 1 Q Well, in Japan, where they consume a lot of fish, in
04:28:06 2 fact, there are many patients with quite low triglycerides,
04:28:09 3 correct?

04:28:09 4 A I don't know the answer to that.

04:28:11 5 Q Okay. Well, let's look at Figure 2, shall we?

04:28:13 6 Figure 2, and the very top one reports triglyceride
04:28:18 7 values for 25 patients in Hayashi, correct?

04:28:23 8 A I'll take your word for it.

04:28:25 9 Q Well, it says n equals 25 at the top, so you don't have
04:28:28 10 to --

04:28:28 11 A I'm sorry. Can you point out --

04:28:31 12 MR. SIPES: Could we blow up the very top graph?

04:28:31 13 BY MR. SIPES:

04:28:34 14 Q You see triglycerides has an N of 25?

04:28:37 15 A Yes.

04:28:38 16 Q And so 25 patients are being reported there for
04:28:43 17 triglycerides, correct?

04:28:44 18 A Yes.

04:28:45 19 Q And all of them are 450 and below, correct?

04:28:50 20 A Yes.

04:28:51 21 Q And, in fact, all but one are below 400.

04:28:56 22 A Yes.

04:28:56 23 Q And all but two are below 350.

04:29:03 24 A Yes.

04:29:05 25 Q And one thing we know is 25 are below 500.

04:29:09 1 A Yes.

04:29:10 2 Q And, of course, there were only 28 patients in Hayashi.

04:29:15 3 A Yes.

04:29:16 4 Q So if there's one thing we know -- I agree Hayashi is a
04:29:19 5 very ambiguous paper, but if there's one thing we know, there
04:29:23 6 were not four or five patients over 500.

04:29:27 7 A I'm not sure that you can make that conclusion from this
04:29:31 8 figure.

04:29:31 9 Q So if there are 25 out of 28 who were 450 or below, that
04:29:37 10 kind of rules out all but three mystery patients, correct?

04:29:42 11 A That's correct.

04:29:43 12 Q Okay. So -- and then the question is what these patients
04:29:49 13 were.

04:29:49 14 Now, one thing we know is they -- that the Hayashi
04:29:53 15 authors used the Friedewald equation to calculate LDL-C.

04:29:53 16 A Yes.

04:29:59 17 Q And the Friedewald equation is not valid for TG values
04:30:04 18 over 400.

04:30:04 19 A Correct.

04:30:04 20 Q So whatever they were doing, they were not measuring
04:30:07 21 LDL-C values for patients over 500, correct?

04:30:10 22 A Yes, I would agree with that.

04:30:12 23 Q Okay. So Hayashi is not telling us anything about the
04:30:15 24 effect of EPA on LDL-C values in severely hypertriglyceridemic
04:30:21 25 patients, correct?

04:30:21 1 A Yes, that's correct.

04:30:29 2 MR. SIPES: Let's look at Mori, which I believe
04:30:31 3 is at DX 1538. And, first, let's look at who the patients
04:30:42 4 were.

04:30:44 5 So, Mr. Brooks, if you'll go to Table 2 and
04:30:47 6 kindly inform me what the exhibit page numbers, I'd appreciate
04:30:47 7 it.

04:30:53 8 So it's page 0004 of DX 1538, Your Honor.

04:30:53 9 BY MR. SIPES:

04:30:58 10 Q So the TG levels for the EPA group was 2.01 in millimoles
04:31:08 11 per liter, correct, Dr. Heinecke?

04:31:13 12 A I'm sure you're correct.

04:31:15 13 Q Okay. And using the handy-dandy conversion of millimoles
04:31:20 14 per liter to milligrams per deciliter of 88.87, that comes out
04:31:27 15 to about 178 milligrams per deciliter in TGs for the EPA
04:31:29 16 group, correct?

04:31:29 17 A Yes.

04:31:30 18 Q Okay. I'm not going claim to have done that in my head.

04:31:34 19 And what that's telling you is these are patients
04:31:38 20 with elevated TGs, but they're not even high TGs, correct?

04:31:42 21 A Yes.

04:31:43 22 Q And, nonetheless, the report was that in administering 4
04:31:49 23 grams of EPA, LDL-C went up 3.5 percent nonstatistical,
04:31:56 24 correct?

04:31:56 25 A It went up nonstatistically significantly, yes.

04:32:00 1 Q And, of course, the number here was small. It was only
04:32:03 2 19 patients in the EPA group, correct?

04:32:09 3 A I would agree it's only 19 patients.

04:32:11 4 Q And it's harder to achieve statistical significance with
04:32:15 5 19 patients than with larger numbers, correct?

04:32:17 6 A Depending on the magnitude of effect, correct.

04:32:20 7 Q Now, of course, Rambjør, which reported an increase in
04:32:24 8 LDL-C from EPA, actually had a larger group of patients
04:32:29 9 administered EPA, correct?

04:32:31 10 A I don't remember the exact number in that, but I'll
04:32:35 11 accept that that's correct.

04:32:36 12 Q Okay. So -- and one thing, of course, that is absolutely
04:32:40 13 clear about Mori is the patients in Mori weren't even high
04:32:44 14 triglycerides, let alone very high triglycerides, correct?

04:32:48 15 A Yes.

04:32:49 16 MR. SIPES: Now, let's look at Kurabayashi.
04:32:53 17 That's DX 1534.

04:32:59 18 Mr. Brooks, if we go to Table 2, which I think
04:33:10 19 is on page 0004.

04:33:10 20 BY MR. SIPES:

04:33:16 21 Q And, again, if we look at the baseline for triglycerides
04:33:20 22 it's, for the EPA group, 135.6, correct?

04:33:25 23 A Yes.

04:33:25 24 Q So Kurabayashi is not even elevated triglycerides,
04:33:29 25 correct?

04:33:30 1 A By the ATP III definition, that's correct.

04:33:35 2 Q It's -- those are normal triglyceride patients, correct?

04:33:38 3 A Yes.

04:33:38 4 Q Now, it's interesting, if you will turn to page 0002,
04:33:53 5 under Materials and Methods, Kurabayashi specifically capped
04:34:00 6 anyone there who was going to -- their upper triglyceride
04:34:03 7 levels, correct?

04:34:04 8 I'll read it to you.

04:34:05 9 MR. SIPES: Mr. Brooks, if you could blow up,
04:34:07 10 under Materials and Methods, the first -- the line that begins
04:34:11 11 -- the paragraph -- excuse me, the sentence that begins
04:34:16 12 "hypertriglyceridemia." It's the second sentence. It's a
04:34:19 13 long sentence. If you could blow it up so it's easier to
04:34:19 14 read.

04:34:19 15 They say,

04:34:22 16 "Hyperlipidemia was defined as a serum total
04:34:30 17 cholesterol concentration of 220 to 280 milligrams
04:34:34 18 per deciliter or a serum triglyceride concentration
04:34:37 19 of 150 to 400 milligrams per deciliter. Women with
04:34:41 20 severe hypertriglyceridemia (serum total cholesterol
04:34:45 21 greater than 280 milligrams per deciliter or serum
04:34:48 22 triglycerides greater than 400 milligrams per
04:34:51 23 deciliter) were considered to have a high risk of
04:34:53 24 coronary heart disease if assigned to the control
04:34:56 25 group."

04:34:56 1 So we set an upper limit of hyperlipidemia in
04:35:00 2 this study, correct?

04:35:01 3 A Yes, that's what it states.

04:35:02 4 Q And this was a study in Japan, correct?

04:35:04 5 A Yes.

04:35:04 6 Q And so what they're saying is we're going to have
04:35:08 7 patients with hyperlipidemia, not with severe hyperlipidemia,
04:35:10 8 correct?

04:35:12 9 A Correct.

04:35:13 10 Q And that meant the upper limit on triglycerides was going
04:35:17 11 to be 400 milligrams per deciliter, correct?

04:35:17 12 A In this study, yes.

04:35:25 13 MR. SIPES: Okay. Let me ask Mr. Brooks to pull
04:35:27 14 up DX 1604.

04:35:27 15 BY MR. SIPES:

04:35:33 16 Q DX 1604 is an article and invited commentary that you
04:35:39 17 published in 2007 in current atherosclerosis reports with your
04:35:46 18 co-author, John Oram, correct?

04:35:47 19 A Yes.

04:35:47 20 Q So this is an article you published, correct?

04:35:50 21 A Yes.

04:35:50 22 MR. SIPES: And I would move DX 1604 into
04:35:54 23 evidence.

04:35:54 24 MR. REIG-PLESSIS: No objection.

04:35:56 25 THE COURT: DX 1604 is admitted.

(Defendants' Exhibit 1604 received in evidence.)

BY MR. SIPES:

Q And so you're writing this as of 2007, correct,
Dr. Heinecke?

A Yes.

Q And you state in the very first sentence,
"Atherosclerotic cardiovascular disease (CVD)
remains the leading cause of morbidity and mortality
in industrialized societies," correct?

A Yes.

Q And that was true in 2008, correct?

A I'm sorry?

Q That was true in 2008?

A Yes.

Q And it's true today.

A Yes, it is.

Q And then going further down, to the last sentence in that
article,

"Even with intensive cholesterol lowering,
however, statins reduce CVD events by only one-third.
This" larger -- excuse me -- "this large residual
disease burden has directed the attention of
biomedical investigators and the pharmaceutical
industry to other potential targets for drug
development."

04:36:56 1 Do you see that?

04:36:56 2 A Yes.

04:36:57 3 Q And let me unpack that. Statins only reduce
04:37:00 4 cardiovascular events by about a third, correct?

04:37:03 5 A Yes.

04:37:04 6 Q That leaves two-thirds of cardiovascular events
04:37:08 7 unaddressed, correct?

04:37:09 8 A Yes.

04:37:10 9 Q And that's heart attacks and strokes and other really bad
04:37:14 10 things that happen to patients, correct?

04:37:15 11 A Yes.

04:37:16 12 Q And, obviously, we want to find something that can deal
04:37:20 13 with that residual cardiovascular risk, even after statin
04:37:24 14 therapy, correct?

04:37:25 15 A Yes.

04:37:26 16 Q And as you note in 2007, people were focused on this
04:37:31 17 problem of residual cardiovascular risk on top of the statin,
04:37:36 18 correct?

04:37:36 19 A Yes.

04:37:37 20 Q And you note in the very next sentence,

04:37:40 21 "One therapeutic target that has generated
04:37:43 22 intense interest is high-density lipoprotein."

04:37:47 23 Do you see that?

04:37:48 24 A Yes.

04:37:48 25 Q Okay. And that was one subject of intense interest,

04:37:52 1 correct?

04:37:52 2 A Yes.

04:37:54 3 Q And you review some evidence about HDL, and then you say,

04:37:59 4 "These findings have led to the widely held

04:38:03 5 view that HDL is cardioprotective and that forcibly

04:38:07 6 raising HDL levels will reduce cardiovascular

04:38:11 7 disease," correct?

04:38:12 8 A Yes.

04:38:12 9 Q And when you say forcibly raising HDL levels, you're

04:38:16 10 talking about, for example, a medical intervention through a

04:38:19 11 drug to raise HDL, correct?

04:38:21 12 A Yes.

04:38:22 13 Q And, in fact, many large pharmaceutical companies try to

04:38:26 14 develop many different therapies, fibrates, niacin, other new

04:38:32 15 agents, to raise HDL and save lives, correct?

04:38:36 16 A That's correct.

04:38:37 17 Q And they all failed.

04:38:39 18 A They all failed?

04:38:40 19 Q There is not a single approved drug to raise HDL by FDA

04:38:46 20 for cardiovascular risk reduction, correct?

04:38:48 21 A That is correct.

04:38:48 22 Q Now, let's go back to Mori. This is, again, DX 1538, and

04:39:10 23 let's look at the Discussion on 0004.

04:39:18 24 Under Discussion Mori says,

04:39:21 25 "This study addressed whether purified EPA

04:39:24 1 and DHA have different effects on serum lipids and
04:39:29 2 lipoproteins, LDL particle size, glucose, and insulin
04:39:32 3 in mildly hyperlipidemic men."

04:39:35 4 Do you see that?

04:39:36 5 A I do.

04:39:37 6 Q They go on,

04:39:37 7 "We found that DHA, but not EPA, improved
04:39:40 8 serum lipid status, in particular a small increase in
04:39:46 9 HDL cholesterol and a significant increase in the
04:39:48 10 HDL-2 cholesterol subfraction, without adverse
04:39:52 11 effects on fasting glucose concentrations."

04:39:54 12 Do you see that?

04:39:55 13 A Yes, I do.

04:39:56 14 Q Now, at a time of intense interest in forcibly raising
04:40:01 15 HDL for cardiovascular reasons, that statement is going to
04:40:04 16 resonate, correct?

04:40:06 17 A What was the year of this publication again? Could I ask
04:40:09 18 that?

04:40:10 19 Q This is Mori 2000, and I want to put your mind into 2008.

04:40:14 20 A Right.

04:40:14 21 Q In 2008, there was an intense interest in HDL, correct?
04:40:17 22 You just wrote that in your own article in 2007.

04:40:21 23 A That's correct, but I'll also point out that there was
04:40:25 24 strong evidence from the first randomized clinical trial using
04:40:29 25 an HDL elevating drug, that it had failed. So there was

04:40:34 1 skepticism about HDLs being a therapeutic target.

04:40:36 2 Q And which agent are you talking about?

04:40:37 3 A Torcetrapib.

04:40:39 4 Q And when did that fail?

04:40:40 5 A I believe it was 2006.

04:40:42 6 Q And you didn't mention that when you mentioned the
04:40:44 7 intense interest in HDL in your 2007 article?

04:40:47 8 A I can't state that. I would have to go back and look at
04:40:51 9 the article to be sure of that.

04:40:53 10 Q And, in fact, other agents being developed by Merck and
04:40:56 11 other companies continued well past 2008, correct?

04:41:00 12 A Yes.

04:41:00 13 Q So that intense interest in HDL, and enormous financial
04:41:05 14 resources and time and patients, were poured into an HDL
04:41:10 15 raising approach to cardiovascular risk well past 2008,
04:41:14 16 correct, Dr. Heinecke?

04:41:16 17 A Yes. That's a fair statement.

04:41:17 18 Q And, in fact, you have devoted a considerable portion of
04:41:21 19 you research life to investigating HDL, correct?

04:41:25 20 A That's very correct.

04:41:27 21 Q Now, one other observation about the difference between
04:41:30 22 DHA and EPA is that EPA appeared to raise fasting glucose, and
04:41:35 23 DHA did not, correct?

04:41:37 24 A Yes.

04:41:37 25 Q Now, I understand your testimony that fasting glucose

04:41:42 1 wasn't important for cardiovascular risk. It is important for
04:41:45 2 patients with diabetes, correct?

04:41:48 3 A Yes.

04:41:49 4 Q And many patients with severe hypertriglyceridemia have
04:41:52 5 diabetes, correct?

04:41:53 6 A Yes.

04:41:53 7 Q And you would not want to develop a treatment for severe
04:41:57 8 hypertriglyceridemia that harmed diabetic patients, correct?

04:42:01 9 A All other things be equal, that's correct.

04:42:14 10 MR. SIPES: Okay. If I could have a moment to
04:42:15 11 confer with my colleague?

04:42:17 12 THE COURT: Yes.

04:42:17 13 (Discussion held off the record.)

04:42:24 14 MR. SIPES: They have helpfully reminded me.

04:42:24 15 BY MR. SIPES:

04:42:26 16 Q You offered some opinions on the prosecution of the
04:42:30 17 patents here, correct?

04:42:33 18 A Yes, I did.

04:42:34 19 Q And you are not a patent law expert.

04:42:37 20 A I am not.

04:42:38 21 Q Are you familiar with the MPEP?

04:42:41 22 A No, I am not.

04:42:42 23 Q Okay. So let me pull up, just to start, with DDX 6.65.
04:43:00 24 This is, I think, the slide you used in your referring to the
04:43:05 25 Notice of Allowance which we'll take a look at it.

04:43:08 1 Do you recall that slide?

04:43:09 2 A Yes, I do.

04:43:10 3 Q Now, it's interesting -- I was very struck by this slide.

04:43:12 4 If you look at it, you've highlighted the examiner's
04:43:15 5 statement,

04:43:16 6 "The prior art does not teach the
04:43:17 7 administration of ethyl-EPA to patients having TG
04:43:22 8 levels between 500 and 1500 milligrams per deciliter
04:43:26 9 (very high).

04:43:28 10 But you didn't highlight the rest of the
04:43:30 11 sentence that says, "As such, there is no anticipation."

04:43:33 12 Isn't that correct?

04:43:34 13 A Yes.

04:43:34 14 Q But, in fact, the examiner's conclusion in the allowance
04:43:38 15 that led to then the analysis of obviousness was that there
04:43:41 16 was no anticipation, correct?

04:43:43 17 A I can't attest to that.

04:43:48 18 Q You're just not a patent law expert.

04:43:50 19 A I'm not a patent lawyer.

04:43:52 20 Q Okay. What is true is you have not expressed the opinion
04:43:54 21 that the patent claims here are anticipated, correct?

04:43:58 22 A I do believe I included the "as such there is no
04:44:03 23 anticipation" in my statement.

04:44:05 24 But I'm not a lawyer, and I'm not offering an
04:44:07 25 opinion on that, that's correct.

04:44:09 1 Q You are not here offering the opinion that the patent
04:44:09 2 claims --

04:44:13 3 A Correct.

04:44:14 4 Q -- at issue in this case are anticipated.

04:44:14 5 A Correct.

04:44:14 6 Q And, in fact, defendants are not asserting that the
04:44:18 7 patent claims are anticipated, correct?

04:44:20 8 A I'm not a lawyer. I can't answer that question.

04:44:22 9 Q Okay. For purposes, as far as you know, the examiner was
04:44:26 10 correct that there's no anticipation here, correct?

04:44:28 11 A I can't answer that question.

04:44:31 12 Q All right. So why don't we look at the Notice of
04:44:45 13 Allowance, which I believe is -- I have PX 380.

04:44:54 14 This is the Notice of Allowance, and if we turn to
04:45:01 15 page PX 380 at 00010 -- first, let's start with 0009, that
04:45:13 16 will get us oriented.

04:45:15 17 It begins, "The prior art teaches," right? And then
04:45:19 18 there's the excerpt you had which says, "as such there is no
04:45:23 19 anticipation."

04:45:24 20 And then it goes on, "However, the prior art
04:45:28 21 teaches."

04:45:28 22 Do you see that?

04:45:29 23 A I do.

04:45:30 24 Q So what happened here is exactly what you would expect.
04:45:33 25 There's no anticipation, as we've all agreed, there's no

04:45:36 1 anticipation, and then the examiner went on to consider
04:45:39 2 obviousness, correct?

04:45:41 3 A Since I'm not clear on what anticipation is, I don't
04:45:45 4 think I'm qualified to answer this question.

04:45:47 5 Q Fair enough.

04:45:47 6 Now, if we go to the next page, 0010, it states,
04:45:53 7 "Applicant was able to overcome the above 103
04:45:57 8 obviousness rejection by showing" --

04:45:59 9 And then it refers to some of the objective
04:46:01 10 indicia of nonobviousness, correct?

04:46:05 11 A That's what the document states.

04:46:05 12 Q Okay. And it goes on to cite declarations from Bays and
04:46:09 13 Weintraub, correct?

04:46:11 14 A I'll assume that that's correct. This is an awful lot of
04:46:18 15 information for me to digest.

04:46:19 16 Q But you are offering opinions on the prosecution here, on
04:46:22 17 this very document.

04:46:24 18 A Yes.

04:46:24 19 Q Okay. The examiner did not cite the Lavin declaration
04:46:32 20 anywhere in the Notice of Allowance, correct?

04:46:34 21 A I can't attest to that. I haven't read through this
04:46:37 22 carefully enough to say.

04:46:39 23 Q At least, in your testimony, you haven't called attention
04:46:41 24 to any discussion about objective indicia that references --
04:46:45 25 or anywhere in the Notice of Allowance that references the

04:46:48 1 Lavin declaration, correct?

04:46:50 2 A I'm not a lawyer. I don't think I'm qualified to comment
04:46:53 3 on these points.

04:46:54 4 Q And for the same reason, you're not familiar with the
04:46:56 5 *Manual of Patent Examining Procedure*, correct?

04:46:59 6 A No, I'm not.

04:47:00 7 Q So you don't know whether or not in fact, under the
04:47:04 8 *Manual of Patent Examining Procedure*, an examiner is supposed
04:47:07 9 to refer to the affidavits on which he or she is relying in
04:47:12 10 issuing a Notice of Allowance, correct?

04:47:15 11 A I'm not qualified to render an opinion on that.

04:47:17 12 Q So you wouldn't know, for example, if MPEP
04:47:21 13 Section 1302.14 IIA would indicate to examiners that they
04:47:28 14 should identify the affidavits that they're relying on,
04:47:31 15 correct?

04:47:32 16 A That's correct.

04:47:32 17 Q Okay. But what -- but, of course, Lavin's declaration
04:47:36 18 doesn't go to the objective indicia of unexpected results or
04:47:40 19 long-felt, unmet need, correct?

04:47:41 20 A I can't offer an opinion on that. I'm not a lawyer.

04:47:48 21 MR. SIPES: All right, sir.

04:47:48 22 Your Honor, with that, I have no further
04:47:50 23 questions.

04:47:50 24 THE COURT: All right.

04:47:50 25

REDIRECT EXAMINATION

BY MR. REIG-PLESSIS:

Q Good afternoon again, Dr. Heinecke.

Do you recall Mr. Sipes asking you several questions about whether you're a cardiologist or a cardiology expert?

A Yes, I do.

Q Is severe hyperlipidemia, in your view, a cardiovascular disease?

A No, it's a metabolic disease.

Q You mentioned you're an endocrinologist. What is endocrinology.

A Endocrinology is the study of metabolism, hormone metabolism, lipoprotein metabolism, many different aspects of hormone signaling, things that regulate lipid levels, and so on and so forth.

Q And is endocrinology a relevant field with respect to the asserted claims in this case and the lipid parameters that we've been discussing?

A In my opinion, yes, since the whole case centers on triglyceride metabolism and the generation of LDL, and these are classically the foci of endocrinologists who study metabolic diseases.

Q Now, do you recall Mr. Sipes asking you about the differences between mixed dyslipidemia and hypertriglyceridemia?

04:49:33 1 A Yes.

04:49:34 2 Q Why are mixed dyslipidemia and hypertriglyceridemia
04:49:36 3 different?

04:49:37 4 A The underlying pathogenesis is very different in those
04:49:41 5 two disorders. In other words, the mechanisms that lead to
04:49:46 6 the elevations of those specific lipoproteins are distinctly
04:49:50 7 different.

04:49:50 8 Q Does the fact that the pathophysiologies of mixed
04:49:56 9 dyslipidemia and severe hypertriglyceridemia are different
04:49:57 10 mean that you would expect those two patient populations to
04:50:01 11 respond differently to lipid therapy?

04:50:03 12 A No, it does not.

04:50:04 13 Q And could you give an example of lipid therapies that
04:50:08 14 would actually act the same between those populations.

04:50:11 15 A As I -- I would, for example, cite a high dose or high
04:50:16 16 potency statin therapy which reduces LDL cholesterol and
04:50:21 17 triglycerides in all patient populations as far as I'm aware.

04:50:25 18 Q And do you recall Mr. Sipes showing you various data from
04:50:29 19 the Tricor label on fibrates?

04:50:32 20 A Yes.

04:50:32 21 Q In your opinion, are the effects of fibrates on LDL-C
04:50:37 22 being different in different populations the general rule for
04:50:43 23 lipid therapies, or an exception to that?

04:50:46 24 A No. I think it's specific for fibric acid derivatives.
04:50:50 25 It has no significance in terms of having implications for

04:50:53 1 other mechanisms -- or, excuse me, other agents that are
04:50:56 2 completely structurally and functionally unrelated to the
04:51:00 3 fibric acid derivatives.

04:51:03 4 MR. REIG-PLESSIS: Mr. Gross, could you pull
04:51:06 5 PX 1026, please. Could you blow-up just the top part of the
04:51:13 6 citation and the title there with the author. Thank you.

04:51:13 7 BY MR. REIG-PLESSIS:

04:51:20 8 Q Dr. Heinecke, do you recall Mr. Sipes asking you about
04:51:23 9 PX 1026, the Carlson paper?

04:51:26 10 A I do.

04:51:27 11 Q What was the date of the Carlson paper?

04:51:30 12 A 1977.

04:51:33 13 Q Was the Carlson paper studying EPA?

04:51:37 14 A No, it did not.

04:51:39 15 Q Was it studying DHA?

04:51:41 16 A No, it was not.

04:51:42 17 Q Was it studying fish oil?

04:51:44 18 A No, it was not.

04:51:46 19 Q What was the Carlson paper studying?

04:51:48 20 A Diet and nicotinic acid.

04:51:52 21 Q And is nicotinic acid also known as niacin?

04:51:56 22 A Yes, it is.

04:51:56 23 Q Is niacin an omega-3 fatty acid?

04:52:00 24 A No, it is not.

04:52:01 25 Q Is it found in fish oil?

04:52:03 1 A No, it is not.

04:52:03 2 Q Is there any structural similarity between niacin and
04:52:07 3 EPA?

04:52:08 4 A None whatsoever.

04:52:10 5 MR. REIG-PLESSIS: Mr. Gross, if we could go to
04:52:12 6 page 3 of PX 1026, and go to the last full paragraph. Just
04:52:20 7 blow that one up, please.

04:52:20 8 BY MR. REIG-PLESSIS:

04:52:23 9 Q According to this paragraph, how many patients with
04:52:27 10 severe hypertriglyceridemia were in the Carlson 1977 paper?

04:52:33 11 A There are nine patients total, and I believe only five
04:52:36 12 were treated with nicotinic acid.

04:52:38 13 Q And would these results in Carlson 1977 on five patients
04:52:43 14 on nicotinic acid have told a person of skill in the art
04:52:48 15 anything about whether EPA would increase LDL-C in patients
04:52:52 16 with severe hypertriglyceridemia?

04:52:53 17 A Not in my opinion.

04:52:58 18 MR. REIG-PLESSIS: Now, Mr. Gross, if we could
04:52:59 19 go to Dr. Heinecke's slides, DDX 6.64.

04:52:59 20 BY MR. REIG-PLESSIS:

04:53:14 21 Q And do you recall Mr. Sipes asking you questions about
04:53:17 22 prior art that was not on your timeline on DDX 6.64?

04:53:22 23 A Yes, I do.

04:53:23 24 Q Was your goal in putting together this timeline to
04:53:26 25 include all prior art on fish oil between 1991 and 2008?

04:53:32 1 A No, it wasn't. The goal of this slide was to present the
04:53:36 2 relevant literature over that time period.

04:53:40 3 Q Would it have been possible for you, in the timeframe
04:53:44 4 that we had an examination today, for you to discuss all of
04:53:47 5 the studies on fish oil conducted between 1991 and 2008?

04:53:53 6 A I don't think so, no.

04:53:55 7 Q How many studies are there on fish oil between 1991 and
04:54:00 8 2008?

04:54:01 9 A It would be a guess at best, but many, many, many
04:54:06 10 publications. Fish oil was an extremely active area of
04:54:10 11 investigation beginning in the '80s.

04:54:12 12 Q Now, do you recall Mr. Sipes specifically asking you
04:54:16 13 about whether certain studies on CNS effects of EPA were on
04:54:22 14 your timeline?

04:54:22 15 A Yes.

04:54:23 16 Q And what are CNS effects?

04:54:25 17 A CNS is the central nervous system, so that would be your
04:54:30 18 brain.

04:54:31 19 Q And do you consider studies on the CNS effects of EPA
04:54:37 20 particularly relevant to whether EPA is an effective treatment
04:54:40 21 on reducing triglycerides?

04:54:41 22 A I'm aware of no connection whatsoever between those
04:54:45 23 things.

04:54:46 24 Q So was there any reason, in your view, to include those
04:54:49 25 studies in a timeline of relevant prior art?

04:54:52 1 A I wasn't even aware of it, and I'm very familiar with the
04:54:55 2 literature, so I would have to say that I don't think that's
04:54:58 3 relevant.

04:54:59 4 Q Now, do you recall counsel -- or Mr. Sipes asking you
04:55:14 5 questions about whether the mechanism of action for EPA was
04:55:18 6 known in 2008?

04:55:19 7 A I do.

04:55:20 8 Q Do you need to know the mechanism of action in order to
04:55:24 9 use a drug clinically?

04:55:26 10 A No, you do not. I think fish oil is a perfect example of
04:55:29 11 that.

04:55:30 12 Q And I think you started to mention this on your
04:55:33 13 cross-examination, but is there a possible mechanism of action
04:55:36 14 for EPA that is consistent with the clinical data and the
04:55:44 15 prior art on its effects on LDL-C?

04:55:44 16 A I have offered one potential mechanism, which would be
04:55:48 17 the reduction of the production of VLDL by the liver.

04:55:52 18 As you may recall, lipoprotein metabolism of apo B
04:55:55 19 containing lipoproteins is relatively simple. It begins with
04:56:00 20 THE production of VLDL. It is then converted to IDL and
04:56:06 21 ultimately to LDL. The LDL, in turn, is primarily cleared by
04:56:06 22 the LDL receptor.

04:56:10 23 So actually it's possible, just from looking at the
04:56:13 24 lipid phenotype, to figure out what the underlying path of
04:56:18 25 physiology might be.

1 What I'm offering is a mechanism that I believe
2 would account for all of the findings of EPA, which are that
3 it would reduce the production of VLDL, so that would lower
4 the triglyceride concentration in the blood.

5 It would lower the production of an IDL, which would
6 lower the concentration of triglycerides and cholesterol in
7 the blood, and, it would lower the concentration of LDL, the
8 topic of our conversation today.

9 And I believe all of those observations are
10 consistent with the idea that you're inhibiting VLDL
11 production by the liver.

12 Q And would that mechanism produce increases in LDL
13 cholesterol in patients with severe hypertriglyceridemia?

14 A It would be effective in any situation, regardless of the
15 underlying path of physiology, because you're reducing the
16 production of the precursor particles of all the particles in
17 the pathway.

18 Q And would that mechanism increase LDL cholesterol while
19 reducing triglycerides?

20 A No. And I would also argue against the idea that you
21 were increasing the conversion of VLDL to IDL and LDL, so --

22 Q Do you recall Mr. Sipes asking you about several
23 references that speculated possible mechanisms for fish oil or
24 omega-3 fatty acids?

25 A Yes.

04:57:37 1 Q In general in the literature, when studies were referring
04:57:41 2 to fish oil or omega-3 fatty acids, was that a reference to
04:57:47 3 purified EPA or to the mixture of EPA and DHA?

04:57:49 4 A Most of the references are to a mixture of DHA and EPA.

04:57:55 5 MR. REIG-PLESSIS: No further questions.

04:57:56 6 Thank you, Dr. Heinecke.

04:57:59 7 MR. SIPES: No questions, Your Honor.

04:58:01 8 THE COURT: I think you may want to confer with
04:58:04 9 counsel.

04:58:05 10 MR. SIPES: Oh, maybe I do have a question.

04:58:05 11 (Discussion held off the record.)

04:58:17 12 MR. SIPES: No questions, Your Honor.

04:58:18 13 THE COURT: All right. Thank you.

04:58:19 14 Thank you, Dr. Heinecke. You may step down.

04:58:21 15 THE WITNESS: Thank you.

04:58:36 16 (The witness was excused.)

04:58:36 17 THE COURT: Well, counsel, how are we doing in
04:58:39 18 terms of time?

04:58:40 19 So I've set aside Friday, next Tuesday, and then
04:58:45 20 the week -- I think it's the last week of January. I can't --
04:58:49 21 last week of January?

04:58:50 22 THE CLERK: Yes.

04:58:52 23 THE COURT: Do you think I can take a break, or
04:58:57 24 should I require that we go until 5:30?

04:59:00 25 MR. SIPES: I think we can take a break, Your

04:59:03 1 Honor.

04:59:03 2 MR. REIG-PLESSIS: Yeah. That's okay.

04:59:06 3 MS. HUTTNER: Yeah, that's fine.

04:59:06 4 THE COURT: All right. So what should I expect
04:59:08 5 for Friday?

04:59:10 6 MS. HUTTNER: Well, Your Honor, we're going to
04:59:13 7 call -- I'm sorry -- our commercial success expert,
04:59:17 8 Mr. Hoffman, and Dr. Fisher on Friday.

04:59:28 9 THE COURT: Well, with that, given that we're on
04:59:31 10 schedule, I'll recess for the day and we'll resume again on
04:59:35 11 Friday as scheduled.

04:59:38 12 MS. HUTTNER: Thank you, Your Honor.

04:59:39 13 (Court adjourned.)

14 -o0o-

15
16 I certify that the foregoing is a correct
17 transcript from the record of proceedings
18 in the above-entitled matter.

19 /s/Kathryn M. French 1/28/2020
20 Kathryn M. French, CCR #392, RPR
21 Official Reporter
22
23
24
25

I N D E X

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